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Hande CELIKER, Haluk KAZOKOGLU, Muhsin ERASLAN, Eren CERMAN, and Levent KARABAS

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Hande CELIKER*, MD, Assistant Professor; Haluk KAZOKOGLU*, MD, Professor; Muhsin ERASLAN*, MD, Associate Professor; Eren CERMAN*, MD, Associate Professor; Levent KARABAS**, MD, Professor

* Marmara University School of Medicine, Department of Ophthalmology, Istanbul, TURKEY
** Kocaeli University School of Medicine, Department of Ophthalmology, Kocaeli, TURKEY

Corresponding Author

Hande Celiker

Address: Marmara University School of Medicine, Department of Ophthalmology Fevzi Çakmak Mah. Muhsin Yazıcıoğlu Cad. No:10 Pendik/Istanbul, TURKEY

Phone: 00 90 5321577740
Fax: 00 90 2166570695

e-mail: drhandeceliker@yahoo.com

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**SUMMARY**

Cat-scratch disease (CSD) is a syndrome which is characterized by lymphadenopathy, fever, and skin lesions in association with a cat scratch or bite. *Bartonella henselae* is the primary bacterial agent responsible for CSD. Here we report serologically proven atypical presentation cases of *B henselae* neuroretinitis. In this study, three neuroretinitis patients were evaluated. Animal contact histories, ocular examinations, systemic work-up, clinical findings, and treatment compliance of the patients were assessed. All the patients denied a history of a cat or any animal contact, or of having CSD findings. Serologic testing with indirect immunofluorescence assay (IFA) was used for diagnosis of Bartonella neuroretinitis. IFA test results were positive for all patients. Two of the patients were treated with antibiotics. Optic disc edema and macular exudates resolved gradually, and at their last follow-up visits, all the signs had disappeared. There was no disease recurrence after finishing treatment. Serious complications were seen in the untreated patient. In conclusion, even though there may be a lack of systemic signs and symptoms of CSD in a patient with neuroretinitis, *B henselae* infection should be considered.
INTRODUCTION

Neuroretinitis (NR) is an uncommon inflammatory optic neuropathy characterized by optic disc swelling and subsequent formation of a partial or complete macular star figure. Cat scratch disease (CSD) has been implicated as a cause of NR which is caused by the gram-negative, aerobic bacillus *Bartonella henselae* (1). CSD typically presents with subacute lymphadenopathy, fever, malaise, chills, and small skin lesions in association with a cat scratch or bite. Contact with infected animals (cat, kitten, or cat fleas) through scratched skin lesions and inoculation with *B henselae* cause CSD (1). Ocular involvement has been estimated to emerge in 5% to 10% of patients with CSD, with NR occurring in 1% to 2% of patients (1,2). Almost all CSD patients state a history of cat contact and about 73% of cases have had a history of traumatic cat exposure (3). At the time of primary *B henselae* infection, a small macule, papule, pustule, or vesicle may form at the inoculation site, which can advance to the systemic reaction characterized by regional lymphadenopathy and the other symptoms (1,4). It is unusual to have ocular findings without systemic CSD (3). This report illustrates serologically proven cases of *B henselae* neuroretinitis which had no signs of systemic involvement and had no cat or animal contact history.

MATERIAL AND METHODS

The study protocol was approved by the local Institutional Ethics Board and conducted according to the tenets of the Declaration of Helsinki. Informed consent was acquired from the patients to allow to practice all kinds of treatment. Uveitis terminology was described by the Standardization of Uveitis Nomenclature (SUN) Working Group (5).

From January 2013 to September 2017, three unilateral neuroretinitis patients were referred to our institute. All of them denied a history of cat scratch, yet all had CSD findings, such as lymphadenopathy, flu-like illness with coryzal symptoms, and dermatological signs. All patients were immunocompetent. Complete ophthalmologic examination, including best corrected visual acuity testing (VA), slit-lamp biomicroscopy, tonometry, and fundoscopy, were performed during the ophthalmic visits. In all cases, the pupils were isocoric and reacted to light in the affected eye. Digital color fundus photographs, and optical coherence tomography
(OCT) were performed at least once and additionally whenever necessary. Presence of macular edema was assessed by OCT and followed. In suitable patients, fundus angiography (FA) was used for the evaluation of posterior segment inflammation. Control of anterior chamber (AC) inflammation was obtained with topical prednisolone acetate 1% every hour per day and topical cyclopentolate hydrochloride 1% twice per day. Patients were evaluated by rheumatology, neurology, and infectious disease consultants. Two of them were treated with empirically systemic antibiotics for the suspicion of CSD at the initial examination. Laboratory work-up was all within normal limits, including complete blood count, biochemistry profile, erythrocyte sedimentation rate, and tuberculin skin test. Serologic studies excluded the presence of *Toxoplasma gondii, Borrelia burgdorferi, Treponema pallidum*, human immunodeficiency virus, and herpes simplex virus. In all cases, serologic testing with indirect immunofluorescence assay (IFA) (EUROIMMUN® Medizinische Labordiagnostika AG, Luebeck Germany) was used for diagnosis of Bartonella neuroretinitis (ranges; IgM >1:16 positive, IgG >1:64 positive). *B henselae* serological test results were positive for all patients. Subsequently, their treatments were switched to convenient antibiotics. *B henselae* serological tests were double-checked by the infectious disease department due to the absence of systemic findings. Patients’ characteristics are summarised in Table 1.

**RESULTS**

**Case 1**

A 21-year-old woman complained of sudden decrease of the vision in right eye (RE) for two weeks. At the initial ophthalmic examination, VA was 20/40 in RE, 20/25 in the left eye (LE). Intraocular pressure (IOP) was 16 mmHg RE and 15 mmHg LE, the slit-lamp examination revealed mild (2+) cells in AC and vitreous of RE, and the AC and vitreous body were normal for LE. Fundus examination of RE revealed optic disc (OD) swelling and macular serous detachment with hard stellate exudates. The left fundus was unremarkable. The macular edema (ME) was confirmed by OCT. FA was normal for LE; RE showed diffuse optic nerve leakage. At the late phase of the angiogram, leakage was noted from the OD toward the fovea. She reported no flu-like symptoms and no lymphadenopathy and had no cats. According to a systemic examination which was performed by an infectious disease consultant, there was no evidence of CSD or any other infectious disease. Parabulbar steroid injection (Depo-Medrol®,
Methylprednisolone Acetate 40 mg/ml., Pfizer, New York, US) was applied to RE. Topical treatment was started for anterior uveitis. Though her follow-up period was scheduled, the patient was not admitted to our clinic until three months later. Titers of *B henselae* antibodies were positive (at a dilution of 1:100 for IgM and 1:512 for IgG). The patient was not treated with any systemic medication due to her delayed control examination. During the follow-up period, the patient suffered from recurrent ME attacks. She was treated with intravitreal anti-vascular endothelial growth factor injections. When IOP increased, anti-glaucomatous medications were used intermittently. At the last ophthalmic examination, VA was 20/25 in both eyes, the slit-lamp examination revealed trace cells in the right AC and no cells in LE, and IOP was 12 mmHg RE and 11 mmHg LE. Fundus examination revealed no remarkable findings for active posterior uveitis in either eye; nevertheless, the epiretinal membrane remained in RE.

**Case 2**

A 20-year-old Chechen male patient complained of acute blurred vision in LE for two weeks. VA was 20/20 in RE, 20/400 in LE. IOP was 14 mmHg in both eyes, the slit-lamp examination revealed no cells in the AC or vitreous bilaterally. Fundus examination of RE was normal. In the LE, OD swelling with a stellate pattern of lipid exudates surrounding the macula was observed. OCT ruled out serous macular detachment, regional lymphadenopathy and flu-like symptoms were absent. He denied being scratched by a cat or any animal. He was diagnosed as suspected Bartonella neuroretinitis and ciprofloxacin (750 mg per day) was initiated. All systemic evaluations were performed and there were no remarkable findings, especially at infectious disease assessment. Titers of *B henselae* antibodies were positive at a dilution of 1:512 for IgM and 1:100 for IgG. According to this serologic result, the treatment was switched to doxycycline (200 mg per day) and rifampicin (600 mg per day) for six weeks. Three weeks later, convalescent serologies were positive for IgM, 1:256, and positive for IgG, 1:320. At a fundoscopic examination, OD swelling and macular exudates partially disappeared in LE (Fig. 1). No severe complications occurred during the follow-up period. At the final ophthalmic examination, VA was 20/20 in both eyes, the slit-lamp examination revealed normal findings in both eyes, and IOP was 14 mmHg RE and 13 mmHg LE. Fundus evaluation was normal in RE. Examination revealed no sequelae findings for the affected eye.
Case 3

A 10-year-old girl presented with loss of vision in LE for one week. VA was 20/20 in RE, 20/100 in LE. IOP was 16 mmHg in both eyes, the slit-lamp examination revealed no cells in the AC or vitreous bilaterally. The right fundus was normal. The left fundus showed OD edema concomitant with macular stellate exudates. The macular serous detachment was detected by OCT and there were hyperreflective dots in the inner retinal layers casting a shadow on the posterior retinal layers and choroid. The child, as well as the parents, denied any previous contact or trauma with a cat. The parents stated that she had no sign of the systemic disease. Azithromycin (400 mg per day for five days) was started due to suspected Bartonella neuroretinitis. According to a pediatric infectious disease specialist, there was no sign of active CSD. Neurological assessment was normal. Titers of*B henselae* antibodies were positive for IgM, 1:128, and positive for IgG, 1:320. Afterwards, the treatment was switched to doxycycline (200 mg per day) and rifampicin (200 mg per day) for six weeks by a pediatric infectious disease specialist. Corticosteroid (CS) (methylprednisolone, 40 mg per day) was added to this antibiotic treatment for two weeks. At the fourth week of the treatment, VA was 20/20 in RE, 20/50 in LE, the slit-lamp examination revealed normal AC findings bilaterally, and IOP was 10 mmHg RE and 11 mmHg LE. Fundus examination was normal in RE, and slight OD edema and reduced macular exudates were present in LE (Fig. 2). At the end of the two years’ follow-up period, there was no recurrence. There was not observed any side effect of the treatment on the child. At the last ophthalmic examination, VA was 20/20 in both eyes, the slit-lamp examination revealed normal findings in both eyes, and IOP was 12 mmHg RE and 15 mmHg LE. Fundus evaluation was normal in RE, while mild OD pallor remained in LE.

**DISCUSSION**

Neuroretinitis is a manifestation of CSD, although in the literature, CSD is reported to be of rare incidence (2,6). The classic clinical diagnosis of CSD necessitates at least three of the following four criteria be met: (1) a history of traumatic cat exposure; (2) a positive skin test of CSD antigen; (3) characteristic regional lymphadenopaties; and (4) negative laboratory examinations for unexplained lymphadenopathy (7-9). None of these criteria were fulfilled in the present cases; nevertheless, it is obvious that all our neuroretinitis patients who were
serologically confirmed were CSD patients. None of the patients experienced traumatic or non-traumatic cat contact. According to our classic knowledge, the main source of infection for cats and also humans seems to be the inoculation of *B. henselae* with a cat scratch. Transmission to humans can also happen with cat biting or cat saliva through an open wound (4). How then can we explain a person who has had no cat contact but is infected, as in the present cases? Although it is very rare, there are such cases in the literature (10-12). Transmission between cats depends on the arthropod vector *Ctenocephalides felis* (*C. felis*) (13). *B. henselae* can reproduce within the digestive system of the *C. felis* and survives several days in the flea feces. The main origin of infection for cats and also humans seems to be the inoculation through a cat scratch by cat claws contaminated with flea feces (14). Flea feces, which contains *B. henselae*, could be transferred through other vectors such as birds, arthropods, flying insects, etc., and inoculation of humans could occur through a small, open wound. In such cases, where a patient has no history of cat contact but exhibits this pathological condition, it might be considered as ‘cat flea transition disease’ instead of CSD. Mucous membranes, such as the conjunctiva, may be the avenue of transmission of the disease (15). Eye rubbing or contact with contaminated cosmetics may lead to direct conjunctival inoculation. But it is not clear whether conjunctival transition can explain the progression of the disease with only eye involvement without systemic effects. It is also noteworthy that for the presented cases there was not only no cat trauma history but also a lack of the systemic findings of CSD. Lymphadenopathy may become chronic and be of long duration; in one recorded case of CSD, adenitis recurred periodically for more than 18 months (16). According to Leith et al., that the patient had no history of exposure of cats made their case more interesting. They assumed that in this case the disease was acquired from a sick bird without the intervention of a cat (11). Ramharter and Kremser reported bilateral Bartonella neuroretinitis accompanied by lymphadenopathy and fever, including cat contact history (17). Metz et al. presented a 6-year-old boy, who admitted frequent contacts with cats, who had lymphadenopathy (18). A case report describes CSD neuroretinitis in a child who presented with pyrexia and cervical lymphadenopathy. She had close contact with cats but she could not recall any cat scratches or bites (19). Kilonback et al. presented a case of neuroretinitis in a woman who had a history of regular cat contact and she experienced flu-like symptoms, headache, and fever (20).

In spite of the fact that *B. henselae* is the most common infectious etiology of neuroretinitis, treatment remains controversial due to the self-limiting nature of the disease. According to two experts, management of Bartonella neuroretinitis is complicated by the rarity of the disease (21).
In the opinion of Lee, antimicrobial therapy shortens the symptomatic illness so that one might consider treating with antibiotics until the laboratory workup is complete. Conversely, according to Bhatti, there was no improved cure rate with treatment. (21). Given the rarity of Bartonella neuroretinitis, however, such a recruitment goal for a randomized controlled trial would be very difficult to accomplish and would require a multicenter study (22). Reed et al reported quicker visual improvement and shortened disease duration with antibiotics (23). Chi et al did not observe an improved visual outcome in treated patients (antibiotics, CS, or both) compared with untreated patients (24). Rostad et al treated an 8-year-old boy with 60 mg oral doxycycline every 12 hours for B. Henselae (25). In the present cases, Case 2 was treated with ciprofloxacin, doxycycline, and rifampicin and Case 3, with CS, was treated with azithromycin, doxycycline, and rifampicin. Case 2 had no disease recurrence after stopping the treatment and no sequelae was noted. Case 1 did not receive any treatment. She had problematic complications. It is obvious that it is not reasonable to decide with a single patient, but serious complications in this small case series were seen only in the untreated patient.

In conclusion, despite the absence of systemic signs and symptoms of CSD in a patient with neuroretinitis, possible B henselae infection should be considered and serological tests should be performed. In our cases, we relied upon IFA for diagnosis. In case of absence of cat or any animal contact history, even if infectious disease specialists and microbiologists think as in a contrast, CSD may have occurred. Thus, four classic criteria of the disease may be revised for the diagnosis. Due to the rarity of Bartonella neuroretinitis, there are a lack of large data series in the literature, therefore, in our opinion, reports of the atypical cases are valuable. We hope that this small case series will lead to larger, controlled, prospective, multicenter studies in the future.

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The authors alone are responsible for the content and writing of the paper
REFERENCES


FIGURE LEGENDS

Fig.1. Color fundus photographs of the Case 2 at the third week of the treatment. Photography of the normal right eye (RE) for comparison. Optic disc swelling disappeared and resolution of the macular stellate pattern was observed in the left eye (LE).

Fig.2. Color fundus photographs of the Case 3 at the fourth week of the treatment. Photography of the normal right eye (RE) for comparison. Optic disc swelling decreased and the macular star exudates which remained only at papillomacular bundle area resolved in the left eye (LE).
Table 1: *The Clinical Characteristics of the Bartonella Neuroretinitis Patients*

Demographic features, systemic and ophthalmic manifestations, treatment modalities and responses were summarized

<table>
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<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tr>
<td><strong>Gender</strong></td>
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<td>F</td>
<td>F</td>
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<td><strong>Systemic findings</strong></td>
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<td><strong>History of cat contact</strong></td>
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<td>Left</td>
<td>Left</td>
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<td>Trace</td>
<td>Trace</td>
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<td>Diffuse</td>
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<td><strong>IFA Titers</strong></td>
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<td>(IgM 1/512; IgG 1/100)</td>
<td>(IgM 1/128; IgG 1/320)</td>
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<td><strong>Initial VA</strong></td>
<td>20/40</td>
<td>20/400</td>
<td>20/100</td>
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<td><strong>Topical Tx</strong></td>
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<tr>
<td><strong>Systemic Tx</strong></td>
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<td>Azt, Dox, Rif, CS</td>
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<tr>
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<td>10</td>
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