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ORIGINAL ARTICLE

Neurological presentations of *Bartonella henselae* infection

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Abstract

Objective Neurological symptoms in patients with cat-scratch disease (CSD) have been rarely reported. The aim of this study is to analyze the frequency of neurological CSD (NCSD) and describe the disease clinical presentation, management and outcome.

Material and methods We retrospectively selected patients with a CSD syndrome and *Bartonella* IgG titers > 1:256. Data regarding epidemiological, clinical, management, and follow-up features were analyzed and discussed. A comparison between NCSD and non-neurological CSD (NNCSD) was established.

Results Thirty-nine CSD patients were selected. NCSD frequency was 10.25%. No children were found affected in the NCSD group. A 65.7% of NNCSD and the entirety of the NCSD group had a history of cat exposure. Immunosuppression was only present in the NNCSD group (8.6%). NCSD presentations were as follows: isolated aseptic meningitis (25%), neuroretinitis (50%), and isolated optic neuritis (25%). A greater proportion of patients in the NCSD group had fever and raised levels of acute phase reactants and white blood cells. 85.7% of NNCSD had a complete recovery, whereas only 50% of the NCSD patients experienced a full recovery.

Conclusion NCSD may be a distinctive group compared to NNCSD due to its later age of presentation, the more intense systemic response, and the poorer outcome.

Keywords Bartonella · Neurobartonellosis · Cat-scratch disease · Neuroretinitis

Introduction

Cat-scratch disease (CSD) is a zoonotic infectious disease caused by *Bartonella henselae*. The disease is usually transmitted to humans via the scratch or bite of cats, its natural reservoir. Epidemiological investigations show that a cat contact history is present in 90% of CSD and the antecedent of scratch or bites is found in 60% of the patients [1].

CSD most often affects children and teenagers (80%), causing a benign, self-limited course disease. Typical CSD consists of a sub-acute regional lymphadenopathy (LAP) accompanied by fever and other systemic symptoms. Atypical

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clinical course or systemic involvement has been described for up to 20% of patients with CSD. Among them, neurological CSD forms have been described in 1 to 7% of cases [2, 3].

A wide spectrum of neurological manifestations have been reported in the literature which, so far, include neuroretinitis and optic neuritis, meningoencephalitis [4], myelitis [5], and acute polyradiculoneuritis [6].

The aim of this study is to analyze the frequency of the neurological manifestations *Bartonella henselae* infection, discuss the clinical findings, management, and follow-up of the disease. Thus, establishing a comparison between NCSD and NNCSD patients.

Material and methods

We retrospectively collected patients with CSD from January 2010 to June 2016. Only patients with a CSD compatible syndrome and immunoglobulin G (IgG) titers greater than 1:256 were selected [7]. The serology method used for all of our patients was indirect fluorescent assay. PCR was only performed in atypical or immunocompromised patients. Three age groups were established: infants (≤ 15 years), adults (16–69), and elderly (≥ 70 years).

Two groups according to the clinical presentation were established: neurological (NCSD) and non-neurological CSD (NNCSD). The compromise of the retina, optic nerve, and remaining central nervous system were considered neurological manifestations. The rest of ocular syndromes were classified as NNCSD.

Data regarding demographics, cat exposure, clinical syndrome and ophthalmological examination, laboratory and neuroimaging workup, treatment, and outcome were collected. A comparison between patients with NCSD and NNCSD presentation was established.

This study is guided by the basic ethical principles in the Declaration of Helsinki. The highest standards of professional conduct will always be maintained and patient confidentiality will be ensured at all times. It will always be applied the national legislation on data protection (Organic Law 15/1999 on Protection of Personal Data).

Results

A total of 39 patients with *Bartonella henselae* infection were selected with no co-infections detected. A positive PCR was found in 1 patient (2.56%) and no culture was done.

Within the NNCSD group, 31 patients (79.5%) had a typical presentation with regional LAP and 4 patients (10.25%) suffered an atypical hepatosplenic disease. A group of four patients (10.25%) had a NCSD presentation (Table 1). Patient 1 was previously published as a single case report [8].

Table 1 Clinical presentation of CSD

	Number of patients (%)
CSD	39
NNCSD	
Typical CSD	31 (79.5%)
Regional lymphadenopathy	31
Atypical CSD	4 (10.25%)
Hepatosplenic disease	4
Osteomyelitis	0
Endocarditis	0
Parinaud's oculoglandular syndrome	0
NCSD	4 (10.25%)
Neuroretinitis/optic neuritis	3 (7.7%)
Meningitis	2 (5.13%)
Encephalitis/myelitis	0

CSD cat scratch disease, *NNCSD* non-neurological CSD, *NCSD* neurological CSD

The mean age was of 42.5 years in the NCSD and of 32.9 in the NNCSD group. Adults were the most affected in both groups (54.3% in the NNCSD and 75% in the NCSD group). While 40% of NNCSD patients were < 15 years, there were no children affected by NSCD.

Male/female proportion was similar in both groups: 65% in NNCSD and 50% in NCSD.

A history of immunosuppression was only present in the NNCSD group (3 patients, 8.6%). A total of 23 patients (65.7%) had a history of cat exposure, while the entirety of NCSD patients had previous exposure to cats. Most patients in both groups had high titers of IgG *Bartonella* serology (> 1/512): 31 (88.6%) in the NNCSD and 3 (75%) in the NCSD group.

A comparison between NCSD and NNCSD patients in some demographic and clinical aspects is summarized in Table 2.

Among the NCSD presentations, patient 1 suffered an aseptic meningitis (25%), patient 2 a unilateral neuroretinitis (25%), patient 3 an optic neuritis (25%), and the last patient (patient 4) a bilateral neuroretinitis with the coexistence of an aseptic meningitis (25%). NCSD patients' clinical characteristics and management are summarized in Table 3. Both neuroretinitis patients developed the CSD characteristic macular star, only after a few days, starting with blurred vision and just an optic disc swelling in the ophthalmoscopic examination. Fundus examination of patients 2–3 are shown in Fig. 1. A greater proportion of patients in the NCSD group had fever and raised levels of blood acute phase reactants as well as white blood cells (WBC). All neurologic CSD patients were studied with a brain MRI (without pathological findings) and CSF analysis.

Table 2 Comparison of demographic, clinical, management, and outcome characteristics in NCSD and NNCSD

	NNCSD	NCSD
	35 (89.75%)	4 (10.25%)
Age (years)	32.9	42.5
Infants (≤ 15 years)	14 (40%)	0
Adults (16–69)	19 (54.3%)	3 (75%)
Elderly (≥ 70 years)	2 (5.7%)	1 (25%)
Sex, male	23 (65.7%)	2 (50%)
Immunosuppression	3 (8.6%)	0
Cats exposure	20 (57.5%)	4 (100%)
Bartonella serology		
1/256–1/512	4 (11.4%)	1 (25%)
> 1/512	31 (88.6%)	3 (75%)
Fever	13 (37.1%)	3 (75%)
↑ESR	7 (20%)	2 (50%)
↑CRP	8 (22.8%)	3 (75%)
↑WBC	5 (14.3%)	2 (50%)
Treatment		
Azithromycin/doxycyclin	20 (57.1%)	0
Azithromycin/doxycyclin + rifampicin	3 (8.6%)	3 (75%)
Other antibiotics (amoxicillin, clarithromycin)	8 (22.9%)	05
Corticoids	0	2 (50%)
No treatment	5 (14.3%)	0
Outcome		
Recovery	30 (85.7%)	2 (50%)
Incomplete recovery/recurrence	5 (14.3%)	2 (50%)

NNCSD non-neurological CSD, NCSD neurological CSD, ESR erythrocyte sedimentation rate (considering elevation ESR > 20 mm), CRP C-reactive protein (considering elevation: CRP > 5 mg/dl), WBC white blood cells (considering elevation > 10.000)

In both groups, azithromycin was the most commonly prescribed antibiotic. In 50% of the patients with NCSD, rifampicin was also added. Full recovery was the most frequent outcome (85.7%) in the NNCSD group, whereas a 50% of the NCSD patients (both patients with neuroretinitis) had a partial recovery, with visual sequelae.

Discussion

The frequency of NCSD in our study is 10.25%, a somewhat higher figure than what other studies have reported [3]. This can likely be explained by the fact that, in our study, neuroretinitis cases were considered neurological rather than ocular manifestations [9].

NNCSD typically affects children and young adults, representing in our study a 40% and 54.3% respectively. However, epidemiology of NCSD is less known. Previous studies have reported a widening in age presentation in systemic and ocular symptoms with respect to typical LAP CSD [10, 11]. In line with this reported growth in age-group, NCSD mainly affected adults between 16 and 69 years old (75%) in our study. Although the severity and presentation of the disease is related to immune status [3, 12], there were no immunosuppressed patients in the NCSD, in comparison to the 8.6% of patients in the NNCSD group.

There are no standardized diagnostic criteria for the definitive diagnosis of CSD or *B. henselae* infections. Moreover, diagnostic testing relies heavily on microbiological analysis. The best initial diagnostic test for CSD is serology, which can be performed with indirect fluorescent or enzyme-linked immunosorbent assays. Although serologic tests have an acceptable sensitivity, they lack specificity because many asymptomatic persons have a positive serology due to previous (often asymptomatic) exposure [7]. Immunoglobulin G (IgG) titers less than 1:64 suggest the patient does not have a current *Bartonella* infection while titers greater than 1:256 strongly suggest active or recent infection. We have chosen the latter IgG threshold to gain specificity [13]. Polymerase chain reaction (PCR) can detect different *Bartonella* species. Although the specificity of PCR is very high, the sensitivity is lower than with serology [14]. Thus, corresponding with the low

Table 3 Neurological CSD patients' characteristics

Patient, sex, age	Cat contact	Neurological symptoms	Systemic symptoms	LA	Initial FE, VA	Control FE	Bartonella serology	↑ESR, CRP	↑WBC	CSF: WBC/mL, P (mg/dL), RBC/mL G(mg/dL) OP(cmH_2O)	MRI	Treatment	Outcome	Diagnosis
Patient 1, male, 74	Yes	Headache	Torticolis fever	Parotid	–	–	IgG 1/3200	-, Yes	Yes	27 (100%M) 55 18 63 < 20	Normal	Doxycyclin + rifampicin	Complete recovery	Aseptic meningitis
Patient 2, male, 34	Yes	Unilateral blurred vision	Myalgias fever	No	Unilateral papilitis, 0,3/1	Unilateral Leber's neuroretinitis*	IgG 1/640, IgM 1/400	Yes, yes	Yes	9 (100%M) 49 20 64 < 20	Normal	Initial MTP pulses Doxycyclin + rifampicin + prednisone	Partial recovery VA: 0,7/1	Neuroretinitis
Patient 3, female, 29	Yes	Ocular pain	None	No	Unilateral optic disk swelling, 1/1	Unilateral optic disk swelling	IgG 1/800	-, No	No	9 (100%M) 44 0 60 < 20	Normal	None	Complete recovery	Optic neuritis
Patient 4, female, 33	Yes	Headache, bilateral blurred vision	Fever	No	Bilateral optic disk swelling, 0.05/0.05	Bilateral Leber's neuroretinitis*	IgG 1/1280	Yes, yes	No	50 (100%M) 44 0 58 25	Normal	Doxycyclin + rifampicin+ dexamethasone	Partial recovery VA: 0,7/0.6	Neuroretinitis aseptic meningitis

LA lymphadenitis, *FE* fundus examination, *VA* visual acuity, *ESR* erythrocyte sedimentation rate (considering elevation ESR > 20 mm), *CRP* C-reactive protein (considering elevation: CRP > 5 mg/dl), *WBC* white blood cells (considering blood elevation > 10.000/mcL), *CSF* cerebrospinal fluid, *P* proteins, *RBC* red blood cells, *G* glucose; *OP* CSF opening pressure; *MRI* nuclear magnetic resonance imaging of the brain, *MTP* methylprednisolone

*Leber's neuroretinitis: optic nerve swelling and macular star

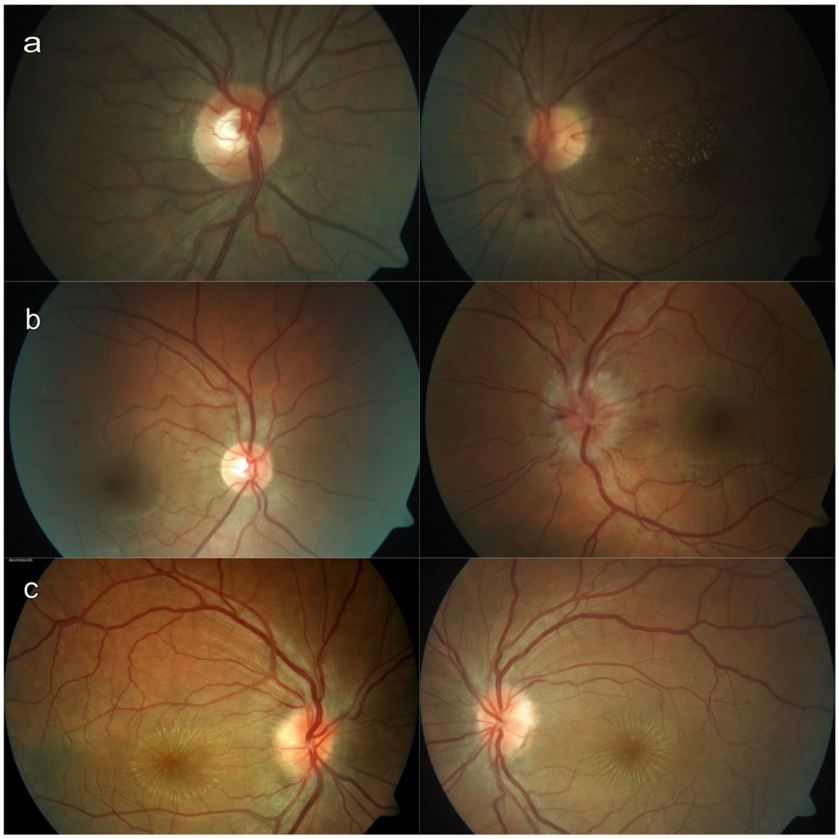

Fig. 1 Fundus examination of patients 2–4. **a** Patient 2, images showing unilateral left Leber's neuroretinitis; **b** Patient 3, images showing unilateral left optic disk swelling; **c** Patient 4, images showing bilateral Leber's neuroretinitis

proportion of positive PCRs found in our study (5.1%). The *Bartonella* species are difficult to culture, and therefore it is not routinely recommended [7].

To date, only one study from the 1960s, by Cathiers et al., has analyzed the frequency of the different neurological manifestations of CSD. Among them, neuroretinitis represented the second most frequent manifestation after encephalitis [15]. In the Breitschwerdt et al. review paper, although neurological CSD incidence is not evaluated, a composite of neurobartonellosis reports is used to discuss a variety of different neurological manifestations in immunocompetent patients [16]. However, the more recent neurological CSD reports are of neuroretinitis cases, with small patient case series [11, 17–19]. In these studies, neuroretinitis is the most common posterior segment complication of ocular CSD, followed by optic disc swelling [11, 17, 19–22].

Despite the typical unilateral presentation of CSD neuroretinitis, bilateral cases, such us in patient 4, have also been described [19–23]. Patients often exhibit a relative afferent pupillary defect, dyschromatopsia, as well as central, cecocentral, or arcuate visual field defects. The typical macular star, distinctive of CSD neuroretinitis, may not be present at the beginning. Over the course of the following 2–3 weeks, the complete Leber's neuroretinitis may become evident or, in around 50% of cases, be absent altogether [21]. For this reason, at the clinical onset, many patients are frequently misdiagnosed as dysimmune optic neuritis and in turn initially treated with methylprednisolone pulses [24–26], as occurred with patient 2. On the other hand, isolated optic neuritis (patient 3) may occur rarely in CSD [27] with specific findings in MRI having been described [28]. Thus, infectious agents like *Bartonella henselae* should be excluded before initiating pulse methylprednisolone therapy for neuroretinitis or optic neuritis, especially in children and young adults.

Encephalopathy was first described as neurological involvement in CSD in the early 1950s [29] with an excellent long-term outcome typically encountered [15]. Over the last few years, various cases of encephalopathy have been reported. These encephalopathy cases include either brainstem [30] or basal ganglia [31] involvement, with ischemia due to a vasculitic complication [32] or status epilepticus in pediatric age [33]. As in our meningitis patients, CSF usually shows mild lymphocytic pleocytosis, with discrete hyperproteinorachia, and normal glucose.

The absence of encephalopathy cases in our study differs with Cathiers et al. results, who reported a nearly 80% incidence of encephalitis in NCSD [15]. This discrepancy could be explained by the more restrictive criteria used in our study when ruling out CSD encephalitis: not only we needed a preserved level of consciousness and no neurological deficits, we demanded the absence of encephalic involvement in the brain MRI.

Half of our NCSD patients had CSF signs of aseptic meningitis contrasting with the anecdotal reports in the literature of

isolated meningitis (without encephalitis) [4, 34] or in the context of neuroretinitis [12, 35].

Other forms of central nervous system involvement may include multiple sclerosis like demyelinating disease [36], acute stroke CNS disease [37], transverse myelitis [5, 6, 38], psychiatric symptoms [39], or even chronic cognitive and gait disorders [40]. Peripheral CSD involvement has also been described as facial neuropathy [41–43] and Guillain Barré syndrome [6, 44].

Previous studies show a 75% of NNCSD patients experience aching, malaise, and anorexia. They also display that 9% of these NNCSD patients may develop low-grade fever [22]. For the neurological patients, the chance of developing a fever greater than 39 °C [15] rose to 50%, which corresponds with our results. Around 50–75% of the NCSD patients in our study experienced elevations of both acute phase serum reactants and leukocytosis, as opposed to only 20% of the NNCSD patients. However, the validity of these results is limited considering our small sample size. Another added difficulty to the detection of CSD, in atypical presentations, is that 75% of our neurological patients did not display lymphadenopathy in their clinical picture.

It has been reported that around 90% of patients with CSD have had some contact with cats [45]. However, our results show a much lower percentage: around 50% in NNCSD but 100% in NCSD patients. This can likely be explained by the fact that this is a retrospective study, based on the review of medical records. Moreover, patients only tend to offer this kind of specific information, such as previous cat exposure, when asked directly.

Treatment of CSD depends on the disease presentation. For typical LAP CSD, a recent meta-analysis study showed that antibiotics failed to significantly affect the cure rate or the time required to achieve recovery [46]. No reliable data is available regarding the benefits of specific antimicrobial therapy for immunocompetent patients with atypical presentations of CSD. For patients with neuroretinitis, the combination of 100 mg of doxycycline twice daily with 300 mg of rifampicin twice daily appears to promote disease resolution, improve visual acuity, decrease optic disk swelling, and decrease the duration of disease [12, 19]. In contrast, Rosen et al. propose that *Bartonella* neuroretinitis is a self-limited disease and requires no antibiotic therapy for its management [47]; although this conclusion is based on a single case experience. The use of systemic corticosteroids is also a subject of debate, due to the slight impact in the course of *Bartonella* neuroretinitis [48]. The same combination of doxycycline and rifampicin, shown to promote the resolution of neuroretinitis, is also suggested for the treatment of *Bartonella* encephalopathy and meningitis [49].

The disease prognosis also depends on the presentation. Neuroretinitis, when treated, typically has a favorable, yet unpredictable outcome [50]. Our study displays that although visual improvement does take place in most patients, vision usually does not return to pre-disease levels. *Bartonella* encephalitis and meningitis seem to have an excellent prognosis. Nevertheless, epileptic status due to *Bartonella* encephalitis and meningitis, tends to be refractory to aggressive anticonvulsant therapy, frequently requiring endotracheal intubation for airway management [33].

Our study on neurological presentations of *Bartonella Henselae* infection has several limitations. Firstly, the retrospective nature of the study limits the amount of information available. Secondly, direct comparison with previous literature is difficult given the relatively small sample size in most studies, including ours. Furthermore, key differences in study design, such as inclusion criteria and the type of serological assay used, contribute to the challenge of relating our results to the previous data.

Conclusions

As neuroretinitis becomes a more recognizable entity, less is known about the other neurological manifestations of CSD, with fewer reports in the literature.

The onset of NCSD at a later age, coupled with a more intense systemic response and a worse outcome, sets the disease apart from NNCSD. Thus, suggesting that NCSD and NNCSD should be perhaps managed differently.

Although *Bartonella Henselae* rarely causes encephalitis and meningitis, their positive prognosis with antibiotic treatment compels the clinician to consider it in the daily practice.

In order to confirm our findings, larger-scaled studies, with a standardized set of both diagnostic criteria and treatment evaluations, are necessary.

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