ORIGINAL RESEARCH

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Evaluation of *Bartonella henselae* IFA Seropositivity in Adult Patients Presenting with Various Symptoms at a Tertiary Education and Research Hospital

Üçüncü Basamak bir Eğitim ve Araştırma Hastanesine Çeşitli Semptomlarla Başvuran Erişkin Hastalarda *Bartonella henselae* IFA Seropozitifliğinin Değerlendirilmesi

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Abstract

Objective: *Bartonella henselae, indirect* , is the etiologic agent of cat scratch disease (CSD). Due to the difficulty of isolation and culture of *Bartonella henselae*, indirect fluorescent antibody (IFA) test is commonly used in diagnosis. In this study, we aimed to investigate the role of serology in the diagnosis of classical and atypical CSD by examining different serological titer values of patients with suspected CSD.

Method: Patients were divided into 2 main groups as negative and positive according to the IFA test result. Patients with positive IFA titer were divided into 2 groups as suspected positive IFA (1:64-1:128) and positive IFA (≥1:256) and subgroup analysis was performed.

Results: A total of 197 patients were included in the study and IFA tests were obtained from the laboratory database. The number of IFA immunoglobulin G seropositive patients was 57 (28.9%). The mean age of the patients was 37 (18-87) years, with 104 (52.8%) being female. While 49.7% of all patients had a history of cat contact, 61.4% of the patients in IFA test positive group had a history of cat contact (p=0.037). The most common symptom was lymphadenopathy (77.7%). Axillary lymphadenopathy was more common in the IFA positive group with a rate of 70.2% (p<0.001). The mean duration of LAP was 1 month in the IFA positive group and 2 months in the IFA negative group with a statistically significant difference (p<0.001). Unilateral LAP was significantly more common in the possible positive IFA group with a rate of 79.1% (p=0.043).

Öz

Amaç: *Bartonella henselae*, kedi tırmığı hastalığının (KTH) etiyolojik etkenidir. *Bartonella henselae*'nin izolasyonu ve kültürünün zorluğu nedeniyle, tanıda dolaylı floresan antikor (İFA) testi yaygın olarak kullanılır. Bu çalışmada, KTH'den şüphelenilen hastaların farklı serolojik titre değerleri incelenerek, klasik ve atipik KTH'nin teşhisinde serolojinin rolü incelendi.

Yöntem: Çalışmaya 01 Ocak 2018-01 Ocak 2024 tarihleri arasında KTH semptomları ile başvuran, 18 yaş üstü hastalar dahil edildi. *Bartonella henselae* İFA test sonucuna göre negatif ve pozitif olarak 2 gruba ayrıldı. İFA titresi pozitif hastalar, şüpheli İFA pozitif (1:64 ve 1:128) ve İFA pozitif (≥1:256) olarak 2 gruba ayrılıp alt grup analizi yapıldı.

Bulgular: Laboratuvar veri tabanından toplam 197 hastada *Bartonella henselae* İFA testleri çalışıldığı saptandı. İFA immünoglobulin G seropozitif hasta sayısı 57 (%28,9) idi. Hastaların yaş ortalaması 37 (18-87) yıl ve 104 (%52,8) hasta kadındı. Tüm hastaların içinde kedi teması öyküsü %49,7'sinde mevcuttu. İFA test sonucu pozitif grubun %61,4'ünde kedi teması saptandı (p=0,037). En yaygın semptom lenfadenopatiydi (%77,7). İFA pozitif grupta aksiller lenfadenopati %70,2 ile daha fazlaydı (p<0,001). İFA pozitif grubun LAP ortalama süresi 1 ay, İFA negatif grubun ise 2 ay olup istatistiksel anlamlı farklılık saptandı (p<0,001). Pozitif İFA grubunda tek taraflı LAP %79,1 oranla anlamlı düzeyde daha fazlaydı (p=0,043).

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Abstract

Conclusion: CSD should be considered in the differential diagnosis of patients with cat contact who present with unilateral lymphadenopathy, especially in the axillary region, as *Bartonella henselae* infection is not uncommon in the population receiving service from our hospital. Although an IFA titer of ≥1/256 supports the diagnosis, it should be kept in mind that a negative IFA result does not exclude the CSD diagnosis.

Keywords: *Bartonella henselae*, cat scratch disease, lymphadenopathy

Öz

Sonuç: *Bartonella henselae* enfeksiyonunun hastanemize başvuran hastalarda nadir olmadığı, kedi teması olan, tek taraflı, özellikle aksiller bölgede lenfadenopati ile başvuran hastaların ayırıcı tanısında KTH akılda tutulmalıdır. İFA titresi ≥1/256 olması tanıyı kuvvetlendirmekle birlikte negatif İFA sonucunun tanıyı dışlamayacağı unutulmamalıdır.

Anahtar kelimeler: *Bartonella henselae*, kedi tırmığı hastalığı, lenfadenopati

Introduction

Bartonella henselae, a Gram-negative bacillus, is the causative agent of cat scratch disease (CSD), which mostly causes self-limiting lymphadenitis but can also lead to more serious clinical manifestations, such as neuroretinitis, encephalitis, visceral organ involvement, and fever of unknown origin (1). In individuals with HIV, *Bartonella henselae* can cause angiomatosis, peliosis hepatis, and splenitis (2).

Epidemiologic studies from different countries have indicated that CSD is distributed worldwide. Although CSD is mostly observed in young individuals, the disease can affect individuals of all ages (3,4).

Cats are natural reservoirs of *Bartonella henselae*, which causes intraerythrocyte bacteremia that can persist for a year or more. Transmission to humans can occur by scratching or biting an infected cat or by exposure to fleas (5).

The isolation and culture of *Bartonella henselae* is difficult; therefore, it is not commonly used for diagnosis. The diagnosis is based on a recent history of contact with cats or fleas in patients with characteristic clinical features. Serological testing for the presence of antibodies against *Bartonella henselae* using indirect fluorescent antibody (IFA) staining is a widely accepted diagnostic procedure for the laboratory diagnosis of cat-scratch disease. The ability of a serologic test to identify patients with a disease (sensitivity) and those without a disease (specificity) is related to the threshold for a positive result. IFA immunoglobulin (Ig) G titers of <1:64 suggest that the patient does not have an active Bartonella infection, titers of 1:64 or 1:128 suggest possible Bartonella infection, and titers of ≥1:256 strongly suggest active or recent infection. However, serologic tests have some limitations, and a negative serologic test does not exclude CSD in patients with characteristic epidemiologic and clinical features (6-8). In addition, cross-reaction between *Bartonella henselae* and *B. quintana, Chlamydia trachomatis, Coxiella burnettii, Rickettsia rickettsii, Ehrlichia chaffeensis, Treponema pallidum, Francisella tularensis*, and *Mycoplasma pneumoniae leads* to false-positive test results especially in IgG assays (8,9).

There are not enough studies on the epidemiology, clinical features, and serological testing of CSD in Turkey. In this study, we aimed to retrospectively review the clinical data of patients with suspected CSD, determine the current epidemiological features, and examine the role of serology in the diagnosis of classical and atypical CSD in adults with different serological titers.

Materials and Methods

This study was conducted with the approval of the University of Health Sciences Turkey Hamidiye Ethics Committee for Clinical Research (01.08.2024, 22.08.2024-24/477).

In this study, we retrospectively examined the data of all patients who were admitted to our hospital's infectious diseases outpatient clinic between January 01, 2018 and January 01, 2024, were over 18 years of age, had diagnostic codes A44.8, A44.9, and A28.1 for bartonellosis and CSD according to the International Classification of Diseases (ICD-10), and underwent the *Bartonella henselae* IFA test. During the relevant period, *B. henselae* IgM testing was not performed in our hospital.

We excluded patients with immunosuppressive conditions or those receiving immunosuppressive therapy.

We obtained demographic data, clinical features, cat contact history, biochemical, microbiological, and radiological test results of the patients from the hospital database. We reviewed clinical data to determine whether the presenting symptoms were related to CSD and laboratory tests for differential diagnoses. We determined whether patients had an alternative diagnosis based on confirmatory laboratory results or a clinician's diagnosis.

Serologic Testing

The presence of *Bartonella henselae* IgG antibodies in serum samples was determined by an IFA assay using a commercial kit (Euroimmun, Germany). After the samples were diluted to 1:64, 1:128, 1:256, 1:512, 1:1024, and 1:2048 in phosphate-buffered saline PBS-Tween buffer (provided in the test kit), the IFA assay was conducted following the manufacturer's protocol. Positive and negative controls were also used. Immunofluorescence was observed using a fluorescence microscope at magnifications of 40X and 200X. A titer of ≥1:256 was considered positive for *Bartonella henselae* IgG. A titer of 1:64 and 1:128 were considered indicative of *Bartonella henselae* IgG (8,10).

Patients were divided into 2 main groups: negative and positive according to the *Bartonella henselae* IFA test result. Patients with positive IFA titers were divided into 2 groups as suspected positive IFA (1:64 and 1:128) and positive IFA (≥1:256) and subgroup analysis was performed.

Statistical Analysis

Patient data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Macos 29.0 (IBM Corp., Armonk, NY) software. Frequency and percentage for categorical variables, median, minimum, and maximum for continuous variables are descriptive values. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. In intergroup comparisons, "Mann-Whitney U test" was used for comparison of continuous variables two groups and "chi-square or Fisher's Exact test" was used for comparison of categorical variables. Results were considered statistically significant at p-value was less than 0.05.

Results

A total of 197 patients who underwent *Bartonella henselae* IFA testing were identified from the laboratory database. The number of IFA IgG seropositive patients was 57 (28.9%). Of the 57 seropositive patients, 12.3% (7/57), 45.6% (26/57), 12.3% (7/57), 14% (8/57), 14% (8/57), and 1.8% (1/57) had titers of 1:64, 1:128, 1:256, 1:512, 1:1024, and 1:2048, respectively.

The mean age of the patients was 37 (18-87) years, with 104 (52.8%) being female. There were no significant differences between age and gender distribution and IFA IgG test results.

History of cat contact was present in 49.7% of the patients. Although 61.4% of the IFA-positive group had cat contact, 45% of the IFA-negative group had cat contact, and this difference was statistically significant (p=0.037).

The most common symptom was lymphadenitis/lymphadenopathy (LAP) (n=153, 77.7%). Axillary lymphadenopathy was significantly more common in the IFA-positive group [70.2% (p<0.001)], whereas cervical lymphadenopathy was significantly more common in the IFA-negative group [54.3% (p=0.026)].

The mean LAP duration was 1 month in the IFA positive group was 1 month and in the IFA negative group was 2 months, and this difference was statistically significant (p<0.001) (Table 1). Lymphadenopathy lasting less than 2 months was significantly more frequent in the IFA-positive group, with a rate of 80.7% (p=0.002). Lymphadenopathy lasting more than 3 months was significantly more frequent in the IFA-negative group (p<0.001).

Of the 25 patients with possible bartonella infection, 24 had a positive IFA test result, which was statistically significant (p=0.001). The demographic, clinical, and laboratory findings of the patients according to the IFA results are presented in Table 1.

Of the 57 IFA-positive patients, 24 patients with IFA titer ≥1:256 were included in the possible-positive IFA group and 33 were included in the suspected-positive IFA group. A subgroup analysis was conducted. Unilateral LAP was significantly more common in the true-positive group. The rate of multiple LAPs was 90.9% and statistically more frequent in the suspected IFA-positive group (p=0.01) (Table 2).

Discussion

Polymerase chain reaction (PCR) analysis of biopsy samples collected from lymph nodes or other infected tissues and isolation of the causative agent in culture is definitive for the diagnosis of bartonellosis. Practical use of these methods is difficult because of the requirement for invasive procedures and limited access to molecular testing. For this reason, serological tests are the first step in the diagnosis of CSD (4,6,11). Clinical interpretation of *Bartonella henselae* serology is challenging due to both low sensitivity and specificity. In this study, we aimed to examine the use of IFA titer value in the diagnosis of CSD in clinical practice by examining clinical findings and other laboratory tests.

In a study conducted in Turkey, the seropositivity rate was found to be 9.9% and no statistical difference was observed between men and women (7). In another recent study conducted in our country, Ergin et al. (9) found that 33.3%

Table 1. Distribution of demographic and clinical findings of patients according to positive and negative test results

Variables		Total (n=197)	IFA negative (n=140)	IFA positive (n=57)	p-value
		n (%) or median (min-max)	n (%) or median (min-max)	n (%) or median (min-max)	
Age (years)		37 (18-87)	37.5 (18-87)	33 (18-72)	0.304
Sex	Male	93 (47.2)	64 (45.7)	29 (50.9)	0.510
	Female	104 (52.8)	76 (54.3)	28 (49.1)	
Cat contact		98 (49.7)	63 (45)	35 (61.4)	**0.037**
Night sweats		27 (13.7)	16 (11.4)	11 (19.3)	0.219
Prior antibiotic use		66 (33.5)	43 (30.7)	23 (40.4)	0.257
Fever		21 (10.7)	13 (9.3)	8 (14)	0.468
Lymphadenopathy	Localized	153 (77.7)	111 (79.3)	42 (73.7)	0.505
	Generalized	44 (22.3)	29 (20.7)	15 (26.3)	
	Unilateral	90 (45.7)	61 (43.6)	29 (50.9)	0.351
	Bilateral	107 (54.3)	79 (56.4)	28 (49.1)	
	Single	42 (21.3)	29 (20.7)	13 (22.8)	0.894
	Multiple	155 (78.7)	111 (79.3)	44 (77.2)	
Region of lymphadenopathy	Cervical	97 (49.2)	76 (54.3)	21 (36.8)	**0.026**
	Axillary	100 (50.8)	60 (42.9)	40 (70.2)	**<0.001**
	Inguinal	52 (26.4)	38 (27.1)	14 (24.6)	0.846
	Supraclavicular	7 (3.6)	4 (2.9)	3 (5.3)	0.415
Duration of lymphadenopathy		1 (1-48)	2 (1-48)	1 (1-24)	**<0.001**
<2 month		125 (63.5)	79 (56.4)	46 (80.7)	**0.002**
>2 month		72 (36.5)	61 (43.6)	11 (19.3)	
<1 month		105 (53.3)	63 (45)	42 (73.7)	**<0.001**
1-3 month		32 (16.2)	23 (16.4)	9 (15.8)	
>1 year		20 (10.2)	18 (12.9)	2 (3.5)	
Size of lymphadenopathy (mm)		24 (5-50)	23 (7-50)	25 (5-50)	0.732
≤20 mm		70 (35.5)	55 (39.3)	15 (26.3)	0.119
>20 mm		127 (64.5)	85 (60.7)	42 (73.7)	
≤40 mm		182 (92.4)	130 (92.9)	52 (91.2)	0.768
>40 mm		15 (7.6)	10 (7.1)	5 (8.8)	
Splenomegaly		10 (5.1)	7 (5)	3 (5.3)	1.000
Hepatomegaly		12 (6.1)	9 (6.4)	3 (5.3)	1.000
WBC (x10^3)		7 (3-20)	7 (3-20)	7 (3.3-13)	0.954
Leukocytosis		22 (11.2)	17 (12.1)	5 (8.8)	0.666
Hemoglobin		13 (5-17)	13 (6-17)	13 (5-16)	0.357
Anemia		36 (18.3)	28 (20)	8 (14)	0.436
PLT (x10^3)		254 (13.2-489)	248 (14.5-489)	264 (13.2-461)	0.267
Thrombocytopenia		5 (2.5)	3 (2.1)	2 (3.5)	0.628
CRP		3 (0-102)	3 (0-102)	4 (0-96)	0.502
CRP > upper limit		70 (35.5)	45 (32.1)	25 (43.9)	0.163
Sedimentation rate		11 (1-120)	11 (1-107)	14 (1-120)	0.547
Sedimentation rate > upper limit		66 (33.5)	49 (35)	17 (29.8)	0.595
Lymph node biopsy histopathology		69 (35)	52 (37.1)	17 (29.8)	0.417
Malignant-atypical		4 (5.8)	4 (7.7)	0 (0)	0.565
Acute inflammation/suppurative/abscess		3 (4.3)	3 (5.8)	0 (0)	0.570
Necrotizing/granulomatous/caseification		36 (52.2)	25 (48.1)	11 (64.7)	0.362
LAP nature in ultrasound					0.439
Benign		150 (76.1)	104 (74.3)	46 (80.7)	
Malign		47 (23.9)	36 (25.7)	11 (19.3)	
Possible Bartonella		25 (12.7)	1 (0.7)	24 (42.1)	**<0.001**

N: Number of patients, IFA: Indirect fluorescent antibody test, CRP: C-reactive protein, WBC: White blood cell, LAP: Lymphadenopathy, PLT: Platelet

Table 2. Distribution of demographic and clinical findings in titer (+) patients according to suspected and positive IFA

Variables		Suspected IFA (n=33)	True positive IFA (n=24)	p-value
		n (%) or median (min-max)	n (%) or median (min-max)	
Age (years)		32 (18-62)	38 (19-72)	0.815
Sex	Male	17 (51.5)	12 (50)	1.000
	Female	16 (48.5)	12 (50)	
Cat contact		21 (63.6)	14 (58.3)	0.896
Night sweats		4 (12.1)	7 (29.2)	0.173
Prior antibiotic use		13 (39.4)	10 (41.7)	1.000
Fever		2 (6.1)	6 (25)	0.059
Lymphadenopathy	Localized	21 (63.6)	21 (87.5)	0.086
	Generalized	12 (36.4)	3 (12.5)	
	Unilateral	11 (33.3)	19 (79.1)	0.043
	Bilateral	22 (66.7)	5 (20.9)	
	Single	3 (9.1)	10 (41.7)	**0.010**
	Multiple	30 (90.9)	14 (58.3)	
Region of lymphadenopathy	Cervical	14 (42.4)	7 (29.2)	0.455
	Axillary	26 (78.8)	14 (58.3)	0.170
	Inguinal	9 (27.3)	5 (20.8)	0.806
	Supraclavicular	1 (3)	2 (8.3)	0.567
Duration of lymphadenopathy		1 (1-24)	1 (1-8)	0.770
<2 month		27 (81.8)	19 (79.2)	1.000
>2 month		6 (18.2)	5 (20.8)	
<1 month		25 (75.8)	17 (70.8)	0.518
1-3 month		4 (12.1)	5 (20.8)	
>1 year		2 (6.1)	0 (0)	
Size of lymphadenopathy (mm)		24 (10-45)	25 (5-50)	0.871
≤20 mm		7 (21.2)	8 (33.3)	0.471
>20 mm		26 (78.8)	16 (66.7)	
≤40 mm		32 (97)	20 (83.3)	0.151
>40 mm		1 (3)	4 (16.7)	
Splenomegaly		2 (6.1)	1 (4.2)	1.000
Hepatomegaly		1 (3)	2 (8.3)	0.567
WBC (x10³)		7 (4-12)	7.4 (3.3-13)	0.554
Leukocytosis		2 (6.1)	3 (12.5)	0.640
Hemoglobin		14 (9-16)	13 (5-16)	0.203
Anemia		3 (9.1)	5 (20.8)	0.261
PLT (x10³)		264 (163-361)	282.5 (13.2-461)	0.518
Thrombocytopenia		0 (0)	2 (8.3)	0.173
CRP		3 (0-96)	4 (0-40)	0.708
CRP > upper limit		15 (45.5)	10 (41.7)	0.989
Sedimentation rate		15 (1-93)	10 (2-120)	0.846
Sedimentation rate > upper limit		9 (27.3)	8 (33.3)	0.841
Lymph node biopsy histopathology		9 (27.3)	8 (33.3)	0.841
Necrotizing/granulomatous/caseification		4 (44.4)	7 (87.5)	0.131
LAP nature in ultrasound				0.326
Benign		25 (75.8)	21 (87.5)	
Malign		8 (24.2)	3 (12.5)	

N: Number of patients, IFA: Indirect fluorescent antibody test, CRP: C-reactive protein, WBC: White blood cell, LAP: Lymphadenopathy, PLT: Platelet

of the samples were positive in antigen evaluation using IFA. Yanagihara et al. (12) reported that 21.3% of 80 patients with suspected CSD were serologically positive for IFA. In a study by Grippi et al. (13), it was reported that seropositivity rates were affected by seasonality (14). In our study, the seropositivity rate was 28.9%. Differences in seropositivity between studies, rates of patients under 18 years of age, seasonality, Bartonella species, and cross-reactivity with *Chlamydia trachomatis*, *Coxiella burnettii*, *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Treponema pallidum*, *Francisella tularensis*, and *Mycoplasma pneumoniae* make it difficult to compare IFA results between populations. In our study, gender and age distribution did not significantly affect the diagnosis of CSD, similar to other studies.

Arıcı et al. (7) reported that 73.9% of seropositive patients had a history of cat contact. Tsuneoka and Tsukahara (15) emphasized that 29 of 30 seropositive patients had cat contact. Another study showed that 40-95% of CSD case series had cat contact (8). In our study, 61.4% of the IFA-positive group and 45% of the IFA-negative group had cat contact, and this difference was statistically significant (p=0.037). In other studies, cat contact was investigated in all CSD suspects. We showed that having a history of cat contact strongly suggested the diagnosis of CSD and that IFA titers were significantly more positive in this patient group. However, it should be considered that the disease can also be transmitted by fleas, and CSD can be diagnosed in patients without a history of cat contact.

A study by Tsuneoka and Tsukahara (15)found that of the 186 seropositive patients, 156 (83.9%) had regional lymphadenopathy. The most common finding in Arıcı et al. (7) study was lymphadenitis (63%). In another study by Tay et al. (10), 74% of patients had unilateral and multiple lymphadenopathies. The most common lymph nodes involved were the cervical and submandibular lymph nodes (10). In our study, the rate of lymphadenopathy was 77.7%. The most common region of lymphadenopathy in the IFA-positive group was axillary lymphadenopathy (70.2% and it was statistically significant). The most common site of lymphadenopathy was the axillary region, consistent with the literature. The differences in the sites of lymphadenopathy involvement between the studies were probably related to the site of bacterial inoculation. However, we could not verify this because of a lack of information about the scratching area in the studies.

Although there was no significant difference in terms of lymphadenopathy size, the duration of LAP was statistically significant at 1 month in the IFA-positive group and 2 months in the IFA-negative group. Among patients with Possible CSD, 80.7% had a LAP duration shorter than 2 months. Similarly, previous studies have shown that the duration of LAP in patients with CSD lasts less than 1 month and mostly resolves spontaneously (11). We believe that it is useful to consider differential diagnoses when the duration of LAP is prolonged.

In our study, 24 patients with IFA titer ≥1:256 were included in the possible positive IFA group. In this group, unilateral LAP was significantly more frequent 79.1%. These findings are consistent with the literature and suggest that lymphadenopathy is located on the side of the inoculated area.

Study Limitations

The limitations of our study include the fact that there were no patients aged under 18 years, PCR was not used in diagnostic samples, and seasonality and inoculation site could not be determined. Patients who were requested for *Bartonella henselae* IgG but whose ICD-10 diagnostic criteria were not recorded may not have been reached. Due to the retrospective nature of the study, conditions that could cause false-positive results for *Bartonella henselae* IFA were excluded.

Conclusion

Our findings show that *Bartonella henselae* infection is not rare in Turkey. The initial symptoms of CSD vary and may cause difficulties for clinicians in making a definitive diagnosis. CSD should always be considered in the differential diagnosis of patients with cat contact and unilateral lymphadenopathy, particularly in the axillary and cervical regions. Although an IFA titer ≥1/256 supports the diagnosis, it must be considered that a negative IFA result does not rule out the possibility of CSD. This study provides important epidemiologic and serologic information about CSD in adult patients in our country; however, further studies using different diagnostic methods are necessary to determine the precise incidence.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Turkey Hamidiye Ethics Committee for Clinical Research (01.08.2024, 22.08.2024-24/477).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: B.S., A.A., Design: B.S., A.A., Data Collection or Processing: B.S., A.A., Analysis or Interpretation: B.S., Literature Search: B.S., A.A., Writing: B.S., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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