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Tularemia in Children: Evaluation of 22 Cases

Çocuklarda Tularemi: 22 Vakanın Değerlendirilmesi

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Abstract

Objective: Tularemia is a highly contagious bacterial zoonotic disease deriving from gram-negative *Francisella tularensis*. The disease is difficult for clinicians, and due to its rarity, a high level of suspicion is required for diagnosis. The purpose of the present study was to retrospectively examine the clinical characteristics, laboratory findings, and responses to treatment of pediatric tularemia cases treated in our clinic.

Material and Methods: Pediatric tularemia cases were included in this retrospective study. The medical records of patients with confirmed diagnoses were examined, and demographic characteristics such as age and gender, presentation symptoms, and risky contact status were recorded. Factors such as living in rural areas, working in agriculture and animal husbandry, similar disease among friends and family, and drinking water sources were examined. Patients' physical and laboratory findings, and medical and surgical treatment results were recorded.

Results: Twenty-two pediatric cases were included in the study, 15 (68.2%) boys and seven (31.8%) girls. The patients were aged mean 12 ± 2.8 (min-max; 3-15 years), and 15 (68.2%) were diagnosed in the fall. The mean time from onset of symptoms to presentation to our hospital was 31.8 ± 20.8 days (min-max; 7-90 days). The most common presentation symptoms were fatigue (54.5%), fever (45.5%), sore throat (%45.5), lack of appetite (40.9%), and abdominal pain-diarrhea (31.8%). Cervical lymphadenopathy (LAP) was determined in all patients at physical examination. Surgical treatment was applied to 18 (81.8%) patients who did not respond to medical treatment [abscess drainage to 14 (63.6%) and LAP excision to four (18.2%)].

Conclusion: Tularemia must be considered in terms of early diagnosis and treatment in children presenting with cervical LAP in endemic regions and not responding to β-lactam and/or macrolide group antibiotics.

Keywords: Children, *Francisella tularensis*, infectious diseases, lymphadenopathy, tularemia

Öz

Giriş: Tularemi, gram-negatif *Francisella tularensis*'ten kaynaklanan oldukça bulaşıcı bakteriyel zoonotik bir hastalıktır. Hastalık klinisyenler için zordur ve nadir görülmesi nedeniyle tanı için yüksek düzeyde şüphe gerekir. Bu çalışmanın amacı, kliniğimizde tedavi edilen pediatrik tularemi olgularının klinik özelliklerini, laboratuvar bulgularını ve tedaviye yanıtlarını geriye dönük olarak incelemektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya pediatrik tularemi olguları dahil edildi. Tanısı doğrulanan hastaların tıbbi kayıtları incelendi ve yaş, cinsiyet gibi demografik özellikleri, başvuru şikayetleri, riskli temas durumu kaydedildi. Kırsal bölgede yaşam, tarım ve hayvancılıkla uğraşma, aile ve çevrede benzer hastalık durumu, içme suyu kaynağı incelendi. Hastaların fizik muayene ve laboratuvar bulguları, medikal ve cerrahi tedavi sonuçları kaydedildi.

Bulgular: Çalışmaya 15 erkek (%68.2) ve yedi kız (%31.8) olmak üzere 22 pediatrik vaka dahil edildi. Hastaların yaş ortalaması 12 ± 2.8 (min-maks; 3-15 yıl)'di ve 15 (%68.2) hasta sonbaharda teşhis edildi. Semptomların başlangıcından hastanemize başvuruya kadar geçen süre ortalama 31.8 ± 20.8 gün (min-maks; 7-90 gün) idi. En sık başvuru semptomları halsizlik (%54.5), ateş (%45.5), boğaz ağrısı (%45.5), iştahsızlık (%40.9) ve karın ağrısı-ishal (%31.8)'di. Fizik muayenede tüm hastalarda servikal lenfadenopati (LAP) belirlendi. Medikal tedaviye yanıt vermeyen 18 (%81.8) hastaya cerrahi tedavi uygulandı (14 [%63.6]'üne apse drenajı ve 4 [%18.2]'üne LAP eksizyonu).

Sonuç: Tularemi, endemik bölgelerde servikal LAP ile başvuran ve β-laktam ve/veya makrolid grubu antibiyotiklere yanıt vermeyen çocuklarda erken tanı ve tedavi açısından düşünülmelidir.

Anahtar Kelimeler: Çocuk, *Francisella tularensis*, enfeksiyon hastalıkları, lenfadenopati, tularemi

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Introduction

Tularemia, also known as 'rabbit fever' or 'deer fly fever,' is a highly contagious bacterial zoonotic disease deriving from gram-negative *Francisella tularensis (F. tularensis)*, an animal pathogen, particularly in rodents (1-3). Due to its high resistance, *F. tularensis* can remain in water and soil for extended periods (3). *F. tularensis* is transmitted through bites from infected animals, direct contact with infected tissue or contaminated soil, inhalation of aerosol organisms, or the consumption of contaminated water and foods (4). In humans it causes a potentially fatal, multisystemic disease. Tularemia is seen in various parts of Europe, particularly the Balkans, Turkey, and Scandinavia (5). While it is more common in rural areas, it can also be seen in cities. The disease can develop at all ages and in both genders (6). No human to human transmission has been reported (3). Since the clinical presentation may assume various forms depending on the entry route of the bacterium, and due to the existence of various subspecies, the disease is difficult for clinicians, and due to its rarity, a high level of suspicion is required for diagnosis (1,3,4). Symptoms in the form of fever, shivering, lethargy, headache, muscle pain, and arthralgia emerge following 1-21 (mean 3-5) days incubation period (3). It has recently attracted attention as the source of an outbreak transmitted from spring water in Turkey and due to its use as a biological weapon (2). There is currently no available vaccine for tularemia.

There are four *F. tularensis* subspecies - *F. tularensis* (type A), *F. holarctica* (type B), *F. mediasiatica*, and *F. novicida*. Most infections in humans and animals are type A or B in origin. Less fatal, type B cases in the form of mild and subclinical disease are generally seen in Europe and Asia (3). Clinical ulceroglandular, glandular, oropharyngeal, oculoglandular, pneumonic, and typhoidal forms exist (7). The ulceroglandular form is more common in Europe, and the oropharyngeal form in Turkey (2). Ulceroglandular and glandular tularemia appear following arthropod vector bites and contact with infected animals (1,4). In ulceroglandular tularemia, regional lymphadenopathy (LAP) occurs characterized by ulceration in the bacterial portal of entry, while LAP without ulceration occurs in the glandular form. Oropharyngeal tularemia appears in the form of severe pharyngitis, following oral intake of contaminated food or water. Oculoglandular tularemia begins with the spread of the bacterium from infected tissue to the conjunctiva. Pneumonic tularemia derives from inhalation of *F. tularensis* and does not respond to empiric antibiotic therapy (1). Typhoidal tularemia is the septic and most severe form, in which localized symptoms are not observed (1,4).

Tularemia is endemic in Turkey and is particularly common in late summer and early fall (8). The purpose of the present study was to retrospectively examine the clinical characteristics, laboratory findings, and responses to treatment of pediatric tularemia cases treated in our clinic.

Materials and Methods

Ethical approval was received from Kastamonu University Clinical Research Ethics Committee in order to conduct the study (Decision No: 2020-KAEK-143-55, Date: 25.02.2021). Informed consent was obtained from parents of the patients who participated in this study. Pediatric tularemia cases presenting to the Erzurum Regional Training and Research Hospital Pediatric Clinic and treated jointly with the Ear Nose Throat (ENT) Clinic between September 2016 and December 2018 were included in this retrospective study. Our hospital, a tertiary health institution, serves patients from Erzurum and surrounding provinces. The majority of our patients live in rural areas and work in animal husbandry. Zoonotic diseases are therefore frequently seen.

Our patients consisted of individuals with findings compatible with tularemia and with specific antibodies determined by the serum microagglutination test (MAT) performed at the Ankara Public Health Laboratory. Patients with a specific antibody titer >1/160 or with four-fold or higher increases at two consecutive titers were regarded as positive (2).

The medical records of patients with confirmed diagnoses were examined, and demographic characteristics such as age and gender, presentation symptoms, and risky contact status were recorded. Factors such as living in rural areas, working in agriculture and animal husbandry, similar disease among friends and family, and drinking water sources were examined. Patients' physical and laboratory findings, and medical and surgical treatment results were recorded.

Patients with fever, LAP, and positive serology were regarded as having glandular tularemia. Patients with findings such as fever, tonsillitis, pharyngitis, and LAP together with positive laboratory findings were regarded as having oropharyngeal tularemia. The only case with conjunctivitis and LAP together with positive serology was recorded as oculoglandular tularemia. A few patients' laboratory findings were unavailable, and complete blood count (CBC), C-reactive protein (CRP), and liver and kidney function test results were examined. Different medical treatment options were present, depending on age (3). 10-days gentamicin (5 mg/kg/day, in two doses, intramuscular (im) or intravenous (iv)), 10-days streptomycin (30 mg/kg/day, in two doses, im), 14-days doxycycline (>8 years) (5 mg/kg/day, in two doses, oral), and 10-14-days ciprofloxacin (15 mg/kg/day, in two doses, oral) were applied in treatment. Cases in which LAP was detected clinically and ultrasonographically and which did not respond to medical treatment were consulted with the ENT clinic, and received surgical treatment. Lymph node aspirate culture from patients undergoing abscess drainage was sent for analysis. Specimens from patients undergoing LAP excision were subjected to histopathological analysis.

Table 1. Demographic data of the patients

Mean age, year	12 ± 2.8	
Gender (%male)	15 (68.2%)	
Symptoms and findings of the patients	n	%
Sore throat	10	45.5
Oral aphthae	4	18.2
Fatigue	12	54.5
Fever	10	45.5
Myalgia	4	18.2
Anorexia	9	40.9
Nause/vomiting	5	22.7
Abdominal pain/diarrhea	7	31.8
Lymphadenopathy	22	100
Conjunctivitis	1	4.5
Skin rash	3	13.6
Water resources used by patients	n	%
Mains water	13	59.1
Fount	6	27.3
Neighborhood fountain	3	13.6
Drinking water chlorination	6	27.3
Month of application to hospital	n	%
April	1	4.5
May	1	4.5
July	2	9.1
August	3	13.6
September	10	45.5
October	3	13.6
November	2	9.1
Tularemia type	n	%
Oropharyngeal	10	45.5
Glandular	11	50
Oculoglanduler	1	4.5

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Version 23.0 (IBM Corporation, Armonk, NY, USA). Numeric variables were expressed as mean ± standard deviation (SD) and median (minimum-maximum) values. Categorical variables were expressed as count and percentage values.

Results

The cases' demographic data are shown in Table 1. Twenty-two pediatric patients aged mean 12 ± 2.8 (min-max; 3-15 years), 15 (68.2%) boys and seven (31.8%) girls, were included in the study. Analysis showed that, 19 (86.4%) patients were older than 10, and only one (4.5%) was under five. In addition, 17 (77.3%) patients lived in rural areas, and 14 (63.6%) worked in agriculture and animal husbandry. Otherwise, 15 (68.2%) patients were diagnosed in the fall. No history of tick bite or travel was present in any patent. A history of contact with lakes or streams was present in eight (36.4%) patients, while contact with game animals was present in only one (4.5%), contact with dead or live animals was present in five (22.7%), and history of contact with rodents or their feces was present in two patients (9.1%). Besides, 16 (72.7%) patients lived in regions where the water was chlorinated irregularly or not at all. Three (13.6%) patients had family histories of tularemia. The mean time from onset of symptoms to presentation to our hospital was 31.8 ± 20.8 days (min-max; 7-90 days). Patients received inadequate treatment (generally β-lactams and/or macrolides) at primary or secondary health institutions prior to correct diagnosis and treatment.

The most common presentation symptoms were fatigue (54.5%), fever (45.5%), sore throat (%45.5), lack of appetite (40.9%), and abdominal pain-diarrhea (31.8%). Erythema nodosum-like skin lesions were observed in three (13.6%) patients. Cervical LAP was determined in all patients at physical examination. Painful LAP was present in 7 (31.8%) patients, multiple LAP in 6 (27.3%), and fluctuating LAP in 11 (50%). The patients' laboratory findings are shown in Table 2.

Treatment modalities are summarized in Table 3. Wound and lymph node aspirate cultures in patients undergoing abscess drainage were negative. Chronic necrotizing granulomatous inflammation was detected at histopathological examination in four patients undergoing LAP excision. No com-

Table 2. Laboratory findings of the patients

Laboratory findings†	Total (n= 22)
WBC (mm^3)	11.368 ± 3.206
ANC (mm^3)	6.404 ± 2575
Hemoglobin (g/dL)	13.3 ± 1.28
PLT (mm^3)	389.000 ± 86.746
CRP (mg/L)	1.32 ± 1.88

†Values are mean ± standart deviation.
WBC: White blood cell, ANC: Absolute neutrophil count, CRP: C-reactive protein.

plications developed during treatment in any patients, and no recurrence was observed at one-year follow-ups.

Discussion

Tularemia is endemic in Turkey (2,5). The first outbreak was seen in Thrace in 1936 (2). Outbreaks and sporadic cases were reported in adults in particular from various different regions in subsequent years (2). Epidemics were reported in Luleburgaz, Tatvan, and Antalya between 1936 and 1953. After an interval of several years, an epidemic subsequently occurred in Bursa in 1988 (9). In recent years, tularemia has become endemic in all areas of Turkey, especially in the Marmara, Western and Central Black Sea and Central Anatolia regions (10). It is thought to be transmitted from frequently contaminated water sources (9). Tularemia has been less frequently reported in children (4). To the best of our knowledge, our cases are the first pediatric case series reported from the region of Erzurum, Turkey.

The majority of cases in one previous study were aged under six, while half of those in another study were younger than 10 (1,5). Otherwise, patients younger than 10 in case series from Turkey are rare (1,5). In a study from Sivas and the surrounding region, 81.4% of patients were older than 10 (2). Two other studies cited rates of 66.7% and 80% (4,11). Similarly in the present study, the majority of patients (86.4%) were aged over 10. This may derive from younger children having less contact with animals and drinking less natural spring water.

Our patients' epidemiological characteristics were consistent with the previous literature (12). Oropharyngeal tularemia rates of 66.7%, 79%, 85.1%, and 90% have been reported in different studies (2,4,5,11). A rate of 27.7% has been reported for glandular tularemia (11). The most common forms in the present study were glandular (50%) and oropharyngeal (45.5%) tularemia. Glandular tularemia is transmitted by contact with animals and arthropod vector bite (3). As in the present study, animal-origin tularemia outbreaks generally occur in late summer and early fall. The high incidence of glandular tularemia in our patients may be due to high rates of living in rural areas (77.3%) and working in agriculture and animal husbandry (63.6%). Oropharyngeal tularemia is associated with contaminated water (5). Our cases of oropharyngeal tularemia may be due to large numbers of patients living in a region where drinking water is not chlorinated regularly, if at all.

The most common finding in tularemia patients is cervical LAP. This was present in 92% of patients in one study (5). LAP was detected in all the patients in the present study. Other common symptoms were fatigue (54.5%), fever (45.5%), and sore throat (45.5%). Cutaneous eruptions can be seen in all clinical forms of tularemia (13). The incidence of erythema nodosum-like cutaneous lesions was compatible with previous studies (4).

Positive culture is the gold standard diagnostic tool in tularemia, and due to the high risk of infection from the laboratory, serological method are employed in diagnosis (2). The most commonly used methods in diagnosis are MAT, tube latex agglutination, and ELISA. Considering the difficulties inherent in microbiological diagnosis, serological diagnosis with clinical presentation is the most widely employed method (1). Cases with MAT> 1/160 are regarded as positive in Turkey (2). Our cases were diagnosed on the basis of clinical findings and MAT positivity. Antibody titers were >1/1280 in half of our cases. This may be due to delayed presentation to our hospital and late diagnosis. WBC count may be normal or elevated in tularemia cases (14). Similar results were also observed in our cases.

Table 3. Treatment modalities of patients

Antibiotics	n	%
Gentamicin	6	27.4
Ciprofloxacin	1	4.5
SAM+streptomycin	1	4.5
Streptomycin	1	4.5
SAM+gentamicin	5	22.8
Gentamicin +ciprofloxacin	5	22.8
Gentamicin+ciprofloxacin+doxycycline	1	4.5
Ciprofloxacin+doxycycline	1	4.5
Gentamicin+ doxycycline	1	4.5
Surgical drainage of fluctuant lymph nodes	14	63.6
Total excision of LAP	4	18.2

SAM: Sulbactam-ampicilin, LAP: Lymphadenopathy.

Early diagnosis and appropriate antimicrobial therapy are highly important in tularemia cases if long-term morbidity and treatment failure are to be avoided (3). Since serology can remain negative for 7-14 days, high clinical suspicion is required for diagnosis (1). Elimination of symptoms and findings and resolution of LAP indicate successful treatment. It is important to success for treatment to be initiated within three weeks after onset of findings (2). β-lactams and macrolides frequently employed in empiric therapy for the treatment of streptococcal pharyngitis and bacterial LAP are not effective in the treatment of tularemia (1,3). One study showed an association between a treatment delay of ≥16 days and spontaneous suppuration (5). Another study showed an abscess formation rate of 62% after a delay in appropriate treatment exceeding three weeks, compared to 38% in case of earlier treatment (15). A delay in treatment after the onset of symptoms greater than one month has also been reported to increase the rate of LAP abscess (16). Reasons for failure in the treatment of tularemia include late initiation of treatment, accompanying chronic disease, and fluctuating LAP before treatment. The high rate of resistance to medical and surgical treatment rate in our cases (81.8%) may be attributable to our patients presenting to us late and to receipt of inappropriate treatment prior to presentation.

Gentamicin, streptomycin, ciprofloxacin, and doxycycline are recommended in the treatment of tularemia. Aminoglycosides such as gentamicin and streptomycin are first-choice drugs (7). Sulbactam-ampicilin (SAM) and gentamicin, was used in five of our patients and SAM and streptomycin in one, and SAM therapy was discontinued in these cases following confirmation of diagnosis of tularemia. Gentamicin is highly effective in tularemia infections in children (1). Gentamicin was used, together with combinations, in 18 (81.8%) of our cases. One pediatric study reported a lack of response to gentamicin of 37.5% (17). No deaths have been reported in tularemia outbreaks in Turkey, with one exception, since 1936 (2). No mortality or recurrence also occurred among any of our patients.

Differential diagnosis of tularemia is quite broad (4). Cervical LAP and abscess can also be seen in tooth infections (18). Glandular tularemia can be confused with syphilis, tuberculosis, cat scratch disease, and toxoplasmosis. Oropharyngeal tularemia can be confused with streptococcal pharyngitis, infectious mononucleosis, adenoviral infection, and diphtheria. Oculoglandular tularemia can be confused with adenoviral infection, cat scratch disease, herpes simplex infection, and syphilis (19). The first diseases to be considered at differential diagnosis of patients presenting with swelling in the neck in regions where tularemia is endemic are primary neoplasms, metastasis, congenital diseases, tuberculosis, and upper airway infections (2). Cases in which chronic granulomatous inflammation or caseous necrosis are determined at histopathological examination in patients undergoing surgical excision can be misinterpreted as tuberculosis and incorrectly treated (20). Chronic necrotizing granulomatous inflammation was detected in four cases undergoing surgical excision in the present study.

This study has a number of limitations. Due to the low patient number, the fact that the four drugs used to treat tularemia were employed alone or in combination in different patients, and the late presentations, no definite conclusion can be drawn about drug efficacy. Further studies involving larger numbers are needed on that subject. In addition, it could not be determined with which subspecies our patients were infected. However, the good prognosis in our patients suggests that were infected with *holarctica* (type B), which is frequently isolated in Europe and Asia (4).

Conclusion

Tularemia must be considered in terms of early diagnosis and treatment in children presenting with cervical LAP in endemic regions and not responding to β-lactam and/or macrolide group antibiotics. Complications in these patients can be prevented through early diagnosis and adequate antimicrobial therapy.

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