Tularemia in children: evaluation of clinical, laboratory and therapeutic features of 27 tularemia cases

Ali Kaya[1], Köksal Deveci[2], İsmail Önder Uysal[3], Ahmet Sami Güven[1], Mevlüt Demir[1], Elif Bilge Uysal[4], Asım Gültekin[1], Füsun Dilara İçağasıoğlu[1]

Departments of [1]Pediatrics, [2]Medical Biochemistry and [3]Otorhinolaryngology, Cumhuriyet University Faculty of Medicine, Sivas, and [4]Department of Medical Microbiology, Sivas State Hospital, Sivas, Turkey

SUMMARY: Kaya A, Deveci K, Uysal İÖ, Güven AS, Demir M, Uysal EB, Gültekin A, İçağasıoğlu FD. Tularemia in children: evaluation of clinical, laboratory and therapeutic features of 27 tularemia cases. Turk J Pediatr 2012; 54: 105-112.

Tularemia is a zoonotic disease caused by *Francisella tularensis*. We aimed to explicate the clinical and laboratory findings of 27 consecutive tularemia patients who were included into the study. The average duration between onset of symptoms and diagnosis was 19.1±7.3 days. Sore throat (100%), fever (93%) and myalgia (100%) were the most frequently observed symptoms, while lymphadenopathy (100%), pharyngeal hyperemia (85%), tonsillitis (74%), and rash (7%) were the most frequently observed physical findings. Treatment failed in 6 patients: 1/13 streptomycin- (changed to doxycycline + streptomycin), 1/7 ciprofloxacin- (changed to streptomycin), and 4/7 gentamicin- (changed to streptomycin) receiving patients who had longer duration to treatment (26.5±2.9 days) than the 21 successfully treated cases (17.0±6.8 days). Tularemia should to be taken into account in the differential diagnosis in cases having tonsillopharyngitis and cervical lymphadenopathy without response to beta lactam/macrolide-group antibiotics in rural areas. We believe that streptomycin should be the first-line antibiotic in the treatment of pediatric tularemia cases, but it should be supported by comprehensive studies with larger patient series.

Key words: Francisella tularensis, outbreak, tularemia, children.

Tularemia is a zoonotic disease caused by *Francisella tularensis,* which is a pathogen of animals, mainly rodents, that can sometimes be transmitted to humans and cause different clinical pictures[1,2]. Recently, tularemia has come to the fore due to outbreaks attributed to spring water in our country and due to its being used as a biological weapon in the world[3,4].

Although it is a disease observed mostly in people living in rural areas, it is also observed rarely in those living in cities. It is of importance that the natural reservoirs of *F. tularensis* are small mammals such as field mouse, field vole, water vole, and rabbits. Animals usually acquire the disease through bites from vectors such as sand flies, ticks, mosquitoes, etc. In humans, tularemia is acquired through various routes, such as bites from vectors, direct contact with an infected animal or infected animal tissues, consumption of infectious animals or contaminated water, and inhalation of infectious particles. Thus, all ages and both genders are at risk of acquiring this disease. The disease acquired by natural means develops after an average incubation period of 3-5 days (range: 1-21 days)[5].

F. tularensis has four subtypes, two of which are clinically and epidemiologically important. *F. tularensis subsp. tularensis* (Jellison type A) originating from rabbits and ticks is seen predominantly in North America and is the most virulent of the four known subspecies. *F. tularensis subsp. holarctica* (Jellison type B), which is clinically milder, is found in Asia and Europe and is considered responsible for waterborne outbreaks. The main clinical forms are oropharyngeal, glandular, ulceroglandular, typhoidal, oculoglandular, and pneumonic tularemia. While the ulceroglandular form is seen in Scandinavian countries in Europe,

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cases reported in Bulgaria, Kosovo and Turkey are mostly oropharyngeal forms[6-8]. Tularemia outbreaks have been reported since 1936 in our country, and the disease has come to attention due to the waterborne outbreaks observed in many regions (such as Konya, Kars, Hatay, Amasya, Tokat, and Çorum), but mainly in Marmara and Karadeniz[9-14].

We believe that this infection is becoming a serious public health problem, as the number of tularemia cases is increasing, and tularemia causes small outbreaks in regions other than those in which it was previously defined. The aim of this study was to explicate the clinical and laboratory findings of the cases and thus to emphasize the importance of the issue in order to draw the attention of pediatricians. Moreover, our cases are the first pediatric tularemia cases reported in Sivas.

Material and Methods

This study was carried out by retrospective evaluation of the files of 27 patients hospitalized and treated in the pediatric service of the Medical Faculty of Cumhuriyet University between 2009 and 2011. Our hospital is a tertiary health center in central Anatolia. It serves a population of about 1 million living primarily on agriculture and animal husbandry. Zoonotic diseases are seen frequently. In our pediatric clinic, inpatient treatment per year is around 2,500 and outpatient around 25,000.

Demographic features, clinical and laboratory findings and follow-up results of the patients were obtained from patient files. Blood samples were taken from those having clinical findings consistent with tularemia, and these samples were sent to Refik Saydam Hıfzısıhha Center, where the microagglutination (MA) test was used for serological diagnosis. Having an antibody titer of ≥1:160 or detection of a four-fold increase in blood samples taken at different times (at least 2 weeks) and presence of clinical findings consistent with tularemia was regarded as acute infection[15,16]. Since the specific recommended security level and special agar for *F. tularensis* is not currently available in our laboratory, specific blood cultures, throat smears and lymph node aspirates could not be studied in our center for isolation of *F. tularensis*.

Empirical antibiotic treatment was started until serology results were obtained for tularemia as: cefazolin sodium (100 mg/kg/day, 3 doses) and gentamicin (5 mg/kg/day, 3 doses), streptomycin (15 mg/kg/day, 2 doses), or ciprofloxacin (15 mg/kg/day, 2 doses). We used ciprofloxacin as a first-line treatment in patients older than 12 years because most of these patients received recommended first-line therapies in their regional primary and secondary health centers. Patients having an antibody titer of ≥1:160 based on serological data were discharged from the hospital after ceasing cefazolin sodium treatment but with continuation of gentamicin, streptomycin or ciprofloxacin treatment up to 14 days.

Recurrent and persistent fever, increase in size of current lymphadenopathy or appearance of new lymphadenopathies, suppuration of lymphadenopathy despite sufficient treatment, and high acute phase proteins were considered as treatment failure[17]. Doxycycline or chloramphenicol + streptomycin or gentamicin treatment was started in patients when treatment failed. Surgical drainage was performed in cases having lymph node fluctuation.

This study was conducted upon approval of the Ethical Committee of Cumhuriyet University Medical Faculty Clinical Studies.

Results

Twenty-seven patients diagnosed with tularemia were included in the study. Six (22%) of these patients were female, while 21 (78%) were male, with an average age of 12.3±3.8 years (3-17 years).

Twenty-six of the patients admitted from Sivas and 1 from Akdağmadeni/Yozgat, and all were living in rural areas. None of the patients had a history of tularemia, tick bite or eating the meat of game animals. However, all our patients were living in rural areas where the spring water was not chlorinated regularly or at all. Drinking water analysis could not be performed as the cases were sporadic.

While the most frequently observed symptoms were sore throat (100%), fever (93%) and myalgia (100%), pharyngeal hyperemia (85%), tonsillitis (74%) and rash (7%) (erythema nodosum-like) were the most frequently observed physical findings. Lymphadenopathy

was in the axillary region in three patients and in the inguinal region in another, while it was in the cervical region and unilateral in other patients (Table I; Fig. 1).

In all our patients, at least one of leukocytes (9446±2675, 4850-14420), C-reactive protein (CRP) (13.01±9.95, 1.5-37.4) or erythrocyte sedimentation rate (ESR) (30.18±15.4, 6-69) was high, while the remainder of the laboratory tests (e.g., hemoglobin [Hb]: 11.81±1.09, 9.8-13.5) were within normal limits (Table I). Brucella, salmonella, toxoplasma, Epstein-Barr virus, cytomegalovirus, parvovirus B19, hepatitis A/B/C, and human immunodeficiency virus (HIV) serology, and anti-streptolysin-O (ASO) tests were negative in all the patients. PPD (purified protein derivative) tests were also negative. Chest radiographs were normal. Aerobic and anaerobic blood culture, urine culture and throat swab cultures were negative for microorganisms other than *F. tularensis*. Two of the 27 patients in whom antibody titers were obtained by MA had a 1:320 titer, while 9 had 1:640, 13 had 1:1280, and 3 had 1:2560 titers.

Four of the patients had glandular tularemia while the other 23 had oropharyngeal tularemia. Patients nos. 15, 16 and 17 in Table II were siblings living in the same house. Distribution of patients in relation to the month of diagnosis was as follows: 5 in January, 5 in February, 6 in March, 6 in April, 2 in September, and 3 in October (Table II). Before the diagnosis as tularemic, all the patients had received a treatment of β-lactam and/or macrolide-group antibiotic by primary and/or secondary healthcare physicians.

The average duration between onset of tularemia symptoms and diagnosis was 19.11±7.3 days (7-32). Treatment failed in 6 patients (22%) whose duration to treatment was longer (26.5±2.9 days [24-32]) than in the 21 successfully treated cases (17.0±6.8 days). Treatment failed in 1/13 cases receiving streptomycin treatment, and treatment was changed to doxycycline + ciprofloxacin. Treatment failed in 1/7 cases receiving ciprofloxacin treatment and in 4/7 patients treated with gentamicin, and the treatments were changed to streptomycin (Table II). In 4 of our patients, we observed lymph node fluctuation during hospitalization. Lymph nodes did not decrease in size, and high laboratory findings (ESR and/or CRP) persisted. These patients were subjected to surgical drainage along with their treatment (Table II), and their histopathological examinations revealed chronic granulomatous inflammation with caseous necrosis.

While the treatment failed in 1 of 13 cases receiving streptomycin treatment, 12 cases were cured. In all the cases, treatment was started within three weeks from the onset of complaints. While the treatment failed in 1 of 7 cases receiving ciprofloxacin treatment, 6 cases were treated successfully. Moreover,

Table I. Clinical and Laboratory Findings of the Patients

Symptoms and Findings	No. (%)
Sore throat	27 (100)
Fever	25 (93)
Myalgia	25 (93)
Lymphadenopathy	27 (100)
Cervical	23 (85)
Axillary	3 (11)
Inguinal	1 (4)
Pharyngeal hyperemia	23 (85)
Tonsillitis	20 (74)
Rash	2 (7)
Erythrocyte sedimentation rate*	21 (78)
C-reactive protein**	15 (56)
Lymphocytosis***	8 (30)
Exitus	0 (0)

* > 20 mm/h, ** > 8 mg/L, *** > 10,000 mm^3

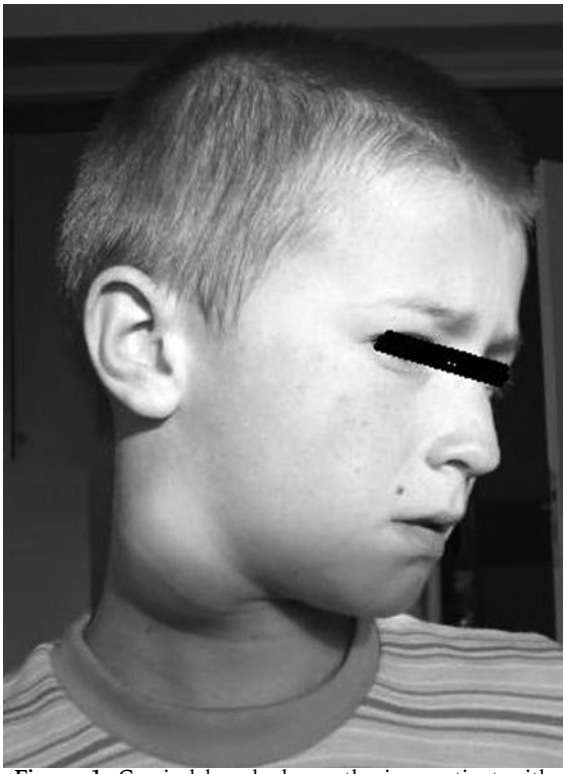

Figure 1. Cervical lymphadenopathy in a patient with tularemia.

it was noteworthy that the treatment was started after three weeks in 5 cases treated successfully. Treatment failure was observed in 4 of 7 patients treated with gentamicin, and treatment was started within three weeks from the onset of complaints in all 7 of these patients. It was noteworthy that 4 of 6 patients in whom treatment failed received gentamicin treatment during hospitalization (Table II).

None of our patients died, and no complications other than scar were observed over a period of six months in the 19 patients who were followed.

Discussion

Tularemia is an endemic disease in Turkey. The first tularemia outbreak was reported in 1936 in the Trakya region. In the years following this outbreak, many epidemic or sporadic cases were reported from different sites in Turkey[6-8,18]. This is the first report of pediatric tularemia from Sivas province.

The main etiological agent of tularemia cases in Europe is *F. tularensis subsp. holarctica*. Its virulence is low and it rarely causes death. The main clinical form of this subspecies is the oropharyngeal form. In our country, many tularemia outbreaks have been reported since 1936. In these epidemics, the oropharyngeal form has been observed to be the most dominant. While one patient was reported to die in one of these epidemics, there were no deaths in the others[3,7,19,20]. In our cases, the oropharyngeal form was also the most common. Our high incidence of the oropharyngeal form of a benign nature without any mortality leads us to think that the type causing tularemia is *F. tularensis subsp. holarctica*. In fact, many studies have reported that isolates in Turkey are consistent with *F. tularensis subsp. holartica*[21,22].

Tularemia outbreaks in our country were characteristically observed to occur during the months following a rainy fall[3,4,23-25]. Similarly, in our region, rain has increased significantly in recent years, and our cases were observed during fall, winter and some spring months. This suggests that rain might have contaminated the water resources.

Regarding the oropharyngeal form, tularemia has been reported to occur in other people among the family of the cases or among those living close to the cases, while contaminated water and food are blamed as the contamination sources[2,10,26]. Likewise, three of our cases were siblings living in the same house, and none of our cases had a history of suspicious animal contact or tick bite. All the cases were consuming spring water that was not chlorinated regularly or at all.

In all forms of tularemia, skin rashes may be seen, such as diffuse maculopapular or vesiculopapular eruptions, pustule, acneiform lesions, erythema nodosum, erythema multiforme, and urticaria[27]. Generally, secondary skin lesions occurring within the first two weeks of the disease and persisting 2-6 weeks are observed more frequently in women than in men. Lesions improve by specific treatment[28,29]. In a study conducted on 74 tularemia cases from the Samsun region, the ratio of erythema nodosum was 3%, while the same ratio was 13% in a study conducted in Bursa[30,31]. Erythema nodosum-like rash was observed in 7% of our cases.

Although the golden standard in diagnosing tularemia is positive culture, usually serological tests are used in the diagnosis

Table II. Important Clinical and Laboratory Findings of the Patients During Hospitalization and Treatment Results

No/ Age(y) /Gender	Clinical Form	MA titer	WBC (mm^3)	CRP (mg/L)	ESR (mm/h)	SB-TB	LAP Drainage	Treatment	2nd Treatment	Month of application to hospital	Result
1/13/E	Oropharyngeal	1/320	8750	31.6	27	14	-	Streptomycin	-	January	Recovered
2/15/K	Oropharyngeal	1/640	13290	18.1	40	25*	+	Ciprofloxacin	-	February	Recovered
3/16/K	Oropharyngeal	1/640	7670	13.1	29	18	-	Streptomycin	-	March	Recovered
4/10/E	Oropharyngeal	1/2560	7460	2.3	33	10	-	Streptomycin	-	March	Recovered
5/12/E	Oropharyngeal	1/2560	9340	5.6	41	15	-	Streptomycin	-	January	Recovered
6/3/E	Oropharyngeal	1/1280	13070	10.7	54	14	-	Streptomycin	-	February	Recovered
7/13/K	Oropharyngeal	1/640	14420	16.2	58	15	-	Ciprofloxacin	-	March	Recovered
8/16/E	Glandular	1/640	9500	24.6	12	27	-	Ciprofloxacin	Streptomycin	January	Recovered
9/4/E	Oropharyngeal	1/640	12980	6.2	33	20	-	Gentamicin	-	April	Recovered
10/17/K	Oropharyngeal	1/1280	7660	4.41	23	25	-	Streptomycin	Doxycycline + Ciprofloxacin	February	Recovered
11/16/E	Oropharyngeal	1/640	11240	17.7	11	12	-	Streptomycin	-	March	Recovered
12/16/E	Oropharyngeal	1/1280	6620	3.1	22	10	-	Streptomycin	-	October	Recovered
13/13/K	Oropharyngeal	1/1280	9430	12.8	26	24	+	Gentamicin	Streptomycin	October	Recovered
14/13/E	Oropharyngeal	1/1280	4850	13.5	69	15	-	Gentamicin	-	February	Recovered
15/17/E	Oropharyngeal	1/1280	7740	1.5	29	25	+	Gentamicin	Streptomycin	September	Recovered
16/14/E	Oropharyngeal	1/1280	12460	2.9	15	20	-	Streptomycin	-	September	Recovered
17/10/E	Oropharyngeal	1/1280	13670	23.4	35	15	-	Streptomycin	-	September	Recovered
18/14/E	Oropharyngeal	1/1280	5710	4.4	30	13	-	Streptomycin	-	March	Recovered
19/14/E	Glandular	1/640	6890	37.4	6	7	-	Ciprofloxacin	-	September	Recovered
20/8/E	Oropharyngeal	1/640	6930	1.9	22	32	+	Gentamicin	Streptomycin	October	Recovered
21/6/K	Oropharyngeal	1/640	9360	15.3	23	15	-	Gentamicin	-	September	Recovered
22/11/E	Oropharyngeal	1/2560	13180	21.9	15	10	-	Streptomycin	-	April	Recovered
23/15/E	Oropharyngeal	1/320	8730	7.1	34	26	+	Gentamicin	Streptomycin	January	Recovered
24/13/E	Glandular	1/1280	6980	29.1	18	30*	+	Ciprofloxacin	-	February	Recovered
25/14/E	Oropharyngeal	1/1280	9270	6.1	23	30*	+	Ciprofloxacin	-	March	Recovered
26/12/E	Glandular	1/1280	8780	4.4	27	30	-	Ciprofloxacin	-	February	Recovered
27/8/E	Oropharyngeal	1/1280	9070	16	60	20*	+	Streptomycin	-	January	Recovered

M: Male. F: Female. MA: Microagglutination. ESR: Erythrocyte sedimentation rate. LAP: Lymphadenopathy. SB-TB: Duration between onset of symptoms and initiation of treatment (days).
* LAP fluctuation was observed during hospitalization and drainage was performed within 7 days after hospitalization.

since the virulence of the microorganism and contamination risk from the laboratory are high. Isolation of bacteria is not routinely recommended. Agglutination test, immunoassay and polymerase chain reaction (PCR) are the most important tests among non-culture methods[1,2,8]. The agglutination test was used to diagnose our cases, and antibody titers of the cases were generally very high, which could be related to the facts that the disease is not sufficiently known by the physicians of the study region, the diagnosis was late, and serum samples were obtained late.

Detection of *F. tularensis* may take up to a couple of weeks during routine microbiological analysis. During the initial laboratory examination, the number of white blood cells changed between 5000 and 22000 per microliter. A minimal increase can be observed in lactic dehydrogenase, serum transaminase and alkaline phosphatase. Increase in serum creatine kinase can be an indicator of rhabdomyolysis[5]. In our patients, high ESR was observed the most frequently, followed by CRP and leukocytes. Other routine laboratory tests were normal.

The differential diagnosis is very important in patients applying with tumors in the neck. In these cases, metastasis, congenital diseases, upper respiratory tract infections, tuberculosis, and primary neoplasms are the first to be considered, while tularemia is not always associated with tumors in the neck if there are no epidemiological data[32,33]. In cases subjected to surgical excision, reporting specimens as chronic granulomatous inflammation or caseous necrosis causes the patient to be examined and treated for tuberculosis[34]. Similarly, histopathological findings of the cases subjected to surgical tuberculosis in our study showed chronic granulomatous inflammation with caseous necrosis. For this reason, tularemia-based epidemics in different regions of our country should be kept in mind in patients applying with a history of mass in the neck and not responding to beta-lactam/macrolide-group antibiotics.

Aminoglycosides such as streptomycin and gentamicin are the first-line drugs in the treatment of tularemia[35,36]. Antibiotics belonging to the tetracycline and chloramphenicol group are also used in the treatment of tularemia, but these are just alternatives to aminoglycosides as they are bacteriostatic. *In vitro* studies carried out in recent years have reported that quinolones are effective on *F. tularensis*, while clinical studies have indicated that they are an alternative treatment for tularemia[37-39]. Although ciprofloxacin has not been licensed for tularemia, it has been started to be used clinically both in children and adults[5]. There is still no successful treatment agent in the oral treatment of pediatric tularemia cases. Oral treatment has gained in importance especially since tularemia was used as a weapon of terror[40]. Streptomycin appears to be the drug of first-line therapy in pediatric tularemia. Treatment failed in more than half of our patients treated with gentamicin, while streptomycin treatment was successful. Similarly, results of treatment with ciprofloxacin were very successful, suggesting ciprofloxacin can be an alternative to streptomycin. However, we believe that this should be supported by comprehensive studies with larger patient series in view of the limited number of our cases.

Treatment success is known as disappearance of symptoms and findings and recovery of affected lymph nodes without suppuration. It has been reported that the treatment is much more successful if started within the first three weeks[8,18]. Consistent with the literature, we obtained very good results in the cases for whom treatment could be started within the first three weeks. This suggests that treatment failure can be closely associated with starting the treatment late. Moreover, we obtained successful results with ciprofloxacin in patients applying after the first three weeks. However, as the number of our cases was small, we believe that this should be supported by comprehensive studies with larger patient series.

In conclusion, tularemia as observed in sporadic and epidemic cases is not a rare disease in our region. It should to be taken into account in the differential diagnosis in cases having tonsillopharyngitis and cervical lymphadenopathy without response to beta lactam/macrolide- group antibiotics with high levels of CRP and/or ESR and in those living or having lived in rural areas. It can be said that, in terms of clinical findings and treatment response, tularemia in children is not very different from that in adults. We believe that streptomycin is the first-line antibiotic

in the treatment of pediatric tularemia cases. Ciprofloxacin treatment showed results as good as those obtained in classical treatment alternatives; however, we believe that this should be supported by comprehensive studies with larger patient series.

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