

Original Article

Epidemiological evaluation of Mediterranean spotted fever in children of the Karak province in south JordanOmar Nafi¹, Yasseen Tarawnah², Amjad Tarawnah¹¹ Pediatric Department, Faculty of Medicine, Mutah University, Karak, Jordan² Disease Control Department, Karak Health Directorate, Ministry of Health, Karak, Jordan**Abstract**

Introduction: The aim of this study was to describe the epidemiological patterns of Mediterranean spotted fever (MSF) as well as its treatment and outcomes in children in south Jordan.

Methodology: A retrospective observational study was conducted from June 2013 to December 2015. Data regarding demographics, clinical presentation, laboratory findings, treatment, and outcomes were collected.

Results: In total, 35 male and 20 female patients (mean age: 6 years \pm 3.6) were included. The incidence of MSF was 7.9 cases/100,000 inhabitants/year; MSF affected 89% of individuals in the summer, 74.5% of those living in a rural area with tent housing, and 100% of those who had contact with animals. All cases presented with fever, and 94.5% had a skin rash. Serological tests were positive in 87.2% of cases, and *Rickettsia conorii* (the Moroccan strain) was present in all positive cases. All cases had thrombocytopenia, but none had leukocytosis. Hyponatremia was present in 71% of cases, and 49%, 61.8%, and 72.7% had increased urea, alanine transaminase, and aspartate aminotransferase levels, respectively. Doxycycline was administered to all patients, with a cure rate of 96.4% and mortality rate of 3.6%.

Conclusions: MSF caused by *R. conorii* (the Moroccan strain) is prevalent in Jordan, and contact with animals is the route of transmission. The patients' responses to doxycycline were excellent. A high index of suspicion, early diagnosis, and specific treatment considerably decrease mortality. MSF should be considered as a possible cause of febrile disease in those with a rash and in those living in rural areas.

Key words: Mediterranean spotted fever; *Rickettsia conorii*; Jordan; children; epidemiology

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Introduction

Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii*. It was first described a century ago as a disease associated with high fever and spots. Conor and Bruch first described the disease in Tunisia in 1910, and it was soon reported in other regions around the Mediterranean basin [1]. *R. conorii* is an obligate intracellular, Gram-negative bacterium that is extremely fastidious [2]. Durand and Conseil proposed the brown dog tick, *Rhipicephalus sanguineus*, as the main vector of the disease [3]; however, other reservoirs are thought to be dogs, rabbits, and some small rodents. On the other hand, humans are an accidental host of *Rickettsia*, and they play no role in maintaining this bacterium in nature. The bacterium can affect individuals of all ages, and it has a seasonal variation related to tick activity; thus, it is more prevalent in hotter months, especially May through September.

After an asymptomatic incubation period (one week), the disease onset is usually abrupt [4]. The

classic clinical triad is composed of a high fever ($> 39^{\circ}\text{C}$); a maculopapular, non-pruriginous rash with palmo-plantar involvement; and an inoculation eschar at the site of the tick bite that can be difficult to identify [5] and may even be absent. Therefore, the diagnosis is based on clinical, epidemiological, and laboratory criteria. However, complete blood count abnormalities are non-specific. For example, leukocytosis, leukopenia, or a normal white blood cell (WBC) count may be present, and thrombocytopenia is frequent. Inflammatory markers (*i.e.*, the sedimentation rate or C-reactive protein level) and liver function tests are usually elevated [2,6,7]. However, a serological test is still the most widely available, easy-to-perform, and frequently used diagnostic method [2,8]. In addition, the Weil-Felix reaction is obsolete [2,9,10], as immunofluorescence is considered the gold standard by the World Health Organization.

Considering that early and appropriate antibiotic treatment is crucial for a favorable outcome [11], clinical evaluation is still the fastest and most valuable

diagnostic tool [10], and a diagnostic scoring system based on epidemiological, clinical, and laboratory data has been developed to help diagnose MSF [6,12]. The treatment for MSF includes antibiotics with a good intracellular activity; doxycycline is preferred. There is still debate regarding the use of tetracyclines in the treatment of MSF in children. Doxycycline is the most effective treatment of all rickettsial diseases. It is the antibiotic recommended by the American Academy of Pediatrics (AAP) and Centers for Disease Control (CDC) for the treatment of suspected rickettsial diseases in patients of all ages.

Clinical improvement usually occurs within 48 hours of treatment initiation, and patients usually recover within 10 days without sequelae. Although reinfection can occur in some patients, MSF is usually an acute disease.

In June 2013, we diagnosed the first recorded case of MSF in Jordan at our facility. Thus, this is the first study of MSF in Jordan, and the aims of the present study were to 1) analyze the epidemiological, clinical, and laboratory characteristics of patients diagnosed with MSF; 2) analyze the efficacy of the drugs administered; and 3) increase the awareness of MSF among pediatricians and physicians in Jordan.

Methodology

All cases diagnosed with MSF and admitted to the pediatric department of Al-karak Hospital in south Jordan over a 30-month period from June 2013 to November 2015 were included. For each patient, epidemiological aspects, such as patient age, patient sex, season, type of housing, and contact with animals, especially for those infected by brown dog ticks, were considered. Clinical data included the presence of fever, skin rash, headache, and vomiting. Regarding laboratory findings, data were collected for WBC count, platelet count, and levels of sodium (Na), urea, and liver enzymes: alanine transaminase (ALT) and aspartate aminotransferase (AST). The type of treatments used and patient outcomes (*i.e.*, the mortality rate) were evaluated. Patients were excluded if they were > 18 years of age or were admitted to another department. The data were analyzed using a simple statistical method that included only age standard deviation and percentages related to epidemiological, clinical, and laboratory findings. Approval from the ethical committee of the Faculty of Medicine, Mutah University, was obtained.

Results

Epidemiology

Fifty-five cases were included during the 30-month period. The incidence rate was 7.9 per 1,000,000 inhabitants. There were 35 male and 20 female patients (mean age: 6 ± 3.5 years), with a male-to-female ratio of 1.75:1.

Regarding the type of housing, 41 cases (74.5%) lived in tents and rural areas, whereas only 14 (25.5%) lived in houses in suburban areas. Contact with animals, especially among those infected by brown dog ticks, was recorded in all cases.

Clinical presentation

A fever was present in 100% of cases. Fifty-two (94.5%) cases had a skin rash, mainly maculopapular, that involved the trunk and extremities. Vomiting and headache were present in 31 cases (56.4%),

Atypical presentations

Two cases had no rash but a high-grade fever and febrile seizures. Cerebrospinal fluid examination was normal in both cases, but the serology tests for *Rickettsia* were positive. A few other cases had a very high titer for *Brucella* in addition to a positive serology for *Rickettsia*.

Laboratory results

Regarding complete blood counts, 56.3% (31/55) of cases had a low WBC count ($< 5 \times 10^9/L$), whereas 43.7% (24/55) of cases had a normal WBC count ($5-10^9/L$). No patients had leukocytosis ($> 10 \times 10^9/L$).

Regarding platelet counts, only 7.2% (4/55) of cases had moderately severe thrombocytopenia ($< 50 \times 10^9/L$), while 38.1% (21/55) had moderate thrombocytopenia ($50-100 \times 10^9/L$) and 54.5% (30/55) had mild thrombocytopenia ($100-150 \times 10^9/L$). Thus, varying degrees of thrombocytopenia were present in all patients. No single case had a thrombocyte count $> 150 \times 10^9/L$.

The most common electrolyte disturbance was hyponatremia; 7.2% (4/55) of cases had an Na level < 125 mEq/L, 25.4% (14/55) had an Na level of 125–130 mEq/L, 38.1% (21/55) had an Na level of 130–135 mEq/L, and 29% (16/55) had a normal Na level.

Urea levels were high in 49% (27/55) of cases. ALT levels were high in 61.8% (34/55) of cases, and AST levels were high in 72.7% (40/55) of cases, as shown in Table 1.

Table 1. Liver enzyme levels among cases infected with Mediterranean spotted fever,

Serum level	< 40 U/L	40–80 U/L	80–120 U/L	120–200 U/L	> 200 U/L
No. of patients (ALT)	21 (38.1%)	22 (40%)	5 (9%)	7 (12.7%)	-----
No. of patients (AST)	15 (27.2%)	27 (49%)	7 (12.7%)	5 (9%)	1 (1.8%)

ALT: alanine transaminase; AST: aspartate aminotransferase

The test used in this study was Vircell *Rickettsia conorii* plate: 96-wells plate coated with *R. conorii* antigen, strain Moroccan(ATCC VR-141) (Vircell S.L., Granada, Spain).

Acute phase serology (i.e., the immunofluorescence assay obtained on admission) was performed for all patients, and was positive in 87.2% (48/55) of cases, equivocal in 7.2% (4/55), and negative in 5.4% (3/55). Identification of the *Rickettsia* serotype (using the American Type Culture Collection VER-141) proved that it was *R. conorii* (the Moroccan strain) in all positive cases.

Treatment and outcomes

Doxycycline at a dose of 3–5 mg/kg was administered to all patients, regardless of age. Clinical improvements were observed within 48 hours of starting treatment. The average hospital stay was 7–8 days.

Total cure was observed in 96.4% (52/55) of patients, and the mortality rate was 3.6% (3/55). Death occurred in these cases because of very late admission after the onset of infection; this led to the development of multiorgan failure, mainly acute renal failure, and severe thrombocytopenia.

Discussion

As in many other Mediterranean countries, no cases of MSF were reported in Jordan before 2013 [13], which is why we thought that rickettsial diseases were not present in our country. In the early spring and summer of 2012, we observed cases that presented with a high-grade fever and skin rash, but no clear diagnoses were made. Some of these cases were so severe that severe thrombocytopenia and multiorgan failure developed; thus, we considered a diagnosis of hemorrhagic fever, but all laboratory work-ups, including polymerase chain reaction assays of several viruses that cause hemorrhagic fever, were negative. However, in the early summer of 2013, a small outbreak of cases occurred among patients who were all living in close contact with animals in the same rural area. Therefore, serological tests were performed for several diseases, including *Rickettsia*, and in June 2013, the

first case of *Rickettsia* was diagnosed at our hospital in Jordan. Since then, we have considered this diagnosis in each case that has presented with a high-grade fever and skin rash. During a 30-month period, we recorded 55 pediatric cases of MSF in our province, with an incidence rate of 7.9 cases per 100,000 inhabitants. This incident rate is higher than that in Spain [14] but lower than that in Bulgaria [15].

MSF is endemic to the Mediterranean area, including northern Africa and southern Europe, and cases are still being identified in new locations within this region. Thus, some cases have recently been reported in Algeria, Malta, Cyprus, Slovenia, Croatia, Kenya, Somalia, and South Africa, in addition to areas surrounding the Black Sea (i.e., Turkey, Bulgaria, and Ukraine) [15–19]. However, it is very interesting that the first reported case of MSF in Jordan was observed and diagnosed in the summer of 2013; before that date, we believed that rickettsial diseases did not exist in Jordan. Epidemiological features, such as the season (particularly summer), contact with animals (particularly dogs), and travel to an endemic area (the Mediterranean Basin), are important in making the diagnosis. In such cases, fever associated with a rash should be considered and treated as MSF [7].

The mean age of patients in this study was only 6 ± 3.6 years because the study was performed in our pediatric department. Most cases occurred in the summer (89% [49/55]), and residing in a tent was associated with infection, as this was the case in 74.5% (41/55) of patients. This is not surprising given that families who rear animals, mainly goats and sheep, leave their village homes during the summer season and live in tents in open areas. Many herders also have dogs; thus, during this time, they are in close contact with these animals. From the epidemiological data, we found that contact with animals occurred in 100% of cases. It is noteworthy that no single case of MSF was recorded during the winter months. Our results are very similar to those of Crespo *et al.* [17] and Rovey and Raoult [13], who reported that MSF was most common during the summer season and that 78% of cases were of rural origin. In addition, clinical presentation was similar to that reported in other countries; all cases had a high-

grade fever, and 94.5% had a maculopapular skin rash that became petechial (except in late and complicated cases with severe thrombocytopenia). Older children (56.4%) were more likely to have associated headache and vomiting.

On the other hand, wide variations in the presence of an eschar have been reported (20%–86%) [7,9]. This may be because the eschar can be difficult to retrieve and can sometimes be atypical (*e.g.*, it has the aspect of a furuncle, which is difficult to recognize). One important difference in the clinical presentation in our cases was the absence of skin eschar in most cases.

Furthermore, the complete blood count evaluation showed thrombocytopenia of varying degrees in 100% of patients, and none had a normal count on admission. However, within two days of starting treatment, we observed dramatic improvements in thrombocyte counts. With regard to leukocyte counts, there was tendency toward leukopenia (56.3%), but no patients had leukocytosis. The most common electrolyte disturbance was hyponatremia. Regarding kidney function, creatinine levels were normal in all patients on admission. However, urea levels were high in 49% (27/55) of patients; this may be explained by dehydration or poor nutrition intake caused by loss of appetite and vomiting during the acute phase of the illness, as levels quickly returned to normal after intravenous fluids were administered. Regarding liver function, ALT levels were high in 61.8% (34/55) of cases, and AST levels were high in 72.7% (40/55), as shown in Table 1.

Interestingly, cases with a negative serology result showed the same favorable response to treatment as the positive cases. Here we have to mention that no molecular methods were used to confirm the identified organism; although this can be a limitation in this study, it could be a strong recommendation for subsequent studies. MSF treatment is based on antibiotics with good intracellular activity, with doxycycline being the most frequently used first-line therapy [4,8]. Alternatives are macrolides, which are particularly useful in pregnant women, and chloramphenicol [2,8,12,20,21]. In our series of cases, doxycycline was administered as the antibiotic treatment in 100% ($n = 55$) of cases, as we did not use other modalities of treatment specific for rickettsia. Clinical improvement occurred within 48 hours of treatment initiation, and patients usually recovered within 5–7 days without sequelae. Cases complicated by sepsis, shock, and multiple organ failure are rare [2,4,8,11,21–24], but they can occur. In the early stages, the diagnosis is clinically based, and if clinical suspicion of rickettsiosis arises,

patients should start appropriate therapy without delay to prevent poor outcomes [11].

The severity of MSF has long been ignored. Although the mortality rate ranged from 1%–3% in early reports, before the antimicrobial drug era, MSF was thought to be a benign illness with a proportion of deaths <1%. MSF was even called benign summer typhus. The first severe case of MSF that resulted in death was reported in France in the 1980s [7], and the first description of a highly severe form of MSF was published in the early 1980s [7]. The incidence rate has since reached as high as 32% in Portugal in 1997.

However, Crespo *et al.* [17] reported that most cases have a favorable outcome, with 5% admitted to the intensive care unit and a mortality rate of 3.6%. In our study, we had a mortality rate of 5.4% (3/55), and acute renal injury, thrombocytopenia, and multiorgan failure were the main causes of death in the three cases of mortality. The reason for our low mortality rate may be related to several factors. First, our patients were young, healthy children without chronic debilitating illnesses. Second, patients presented to the hospital early. Finally, a very high level of awareness of MSF in our department led to a high index of suspicion and the early introduction of specific treatment prior to the serology results. Our results are similar to those of other recent studies [17].

Conclusions

To the best of our knowledge, this is the first study concerning MSF in Jordan. However, MSF is now prevalent in Jordan, and specific and effective treatment is available. MSF in Jordan is caused by *R. conorii* (the Moroccan strain), and contact with animals is a common route of transmission. Patient responses to doxycycline were excellent; thus, a high index of suspicion, early diagnosis, and specific treatment decrease the mortality rate to a very low level. MSF should be considered as a possible cause of febrile disease in those presenting with a rash, particularly in the summer season, and in those living in rural areas.

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