Evaluating Long-Term Health Outcomes in Children with Mediterranean Spotted Fever after Short-Course Doxycycline Therapy: Insights from the Jordanian Experience - A Prospective Cohort Study

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ABSTRACT

Mediterranean spotted fever (MSF) is a tick-borne infection caused by Rickettsia conorii subspecies conorii, transmitted by Rhipicephalus sanguineus. While the acute phase of MSF is well-documented, data on its long-term health outcomes in pediatric patients remain limited. This study evaluates the chronic effects of MSF in children from Al-Karak, Jordan, following a short course of doxycycline. This prospective observational study included pediatric patients diagnosed with MSF through ELISA. Follow-ups involved structured questionnaires, physical examinations, and laboratory assessments of inflammatory markers, blood counts, liver enzymes, creatine phosphokinase, creatinine, calcium, and electrolytes. Growth parameters (height, weight, BMI, Z-scores) and clinical outcomes were analyzed. Most participants were from urban areas with frequent exposure to sheep and dogs. Biochemical analyses were generally normal in most cases, except for a few cases with mild elevation of liver enzymes, and coagulation factors. Notably, 76% of cases showed elevated creatine phosphokinase levels. New complaints included asthma, tonsillitis, and otitis media in 6% of patients, while 12% reported recurrent fever and 10% experienced recurrent rash. Growth parameters remained within normal ranges, and school performance was predominantly excellent. Physical examinations showed no significant chronic abnormalities. This study provides new insights into the long-term health outcomes of pediatric MSF patients following a short course of doxycycline. While most findings were favorable, some biochemical deviations and new complaints highlight the importance of continued monitoring. Understanding the chronic effects of MSF can improve long-term patient care and guide future research on the disease's lasting impact.

Keywords: chronic complications, long-term outcomes, pediatric MSF, Rickettsia conorii, short-course doxycycline

INTRODUCTION

Mediterranean spotted fever (MSF), a tick-borne rickettsiosis caused by Rickettsia conorii subspecies conorii, is a significant public health concern in the Mediterranean region, including Jordan[1]. The primary vector of this bacterium is the brown dog tick, Rhipicephalus sanguineus, with both the tick and the canine population serving as crucial reservoirs[2,3]. Clinically, MSF typically presents with a "tache noire" (a characteristic eschar), maculopapular rash, and fever, with the potential to progress to severe multiorgan involvement due to the bacterium's predilection for endothelial cells, leading to widespread vascular injury and inflammation[4].

In recent years, the incidence of MSF has been on the rise in several parts of the Mediterranean basin, including the Al-Karak region of Jordan, which is particularly vulnerable due to its climate and the prevalence of stray dogs that maintain the tick population[5]. Despite the increasing number of cases, there is a significant gap in the literature regarding the long-term outcomes of patients who recover from MSF, especially among pediatric populations. This gap is concerning given the potential for chronic complications, including persistent vascular inflammation, which can predispose patients to long-term cardiovascular issues such as coronary artery disease and peripheral vascular disorders[6,7]. Additionally, neurological sequelae, such as cognitive impairments and chronic fatigue, have been observed following other rickettsial

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infections, raising concerns about similar long-term outcomes in MSF patients[8,9].

The current body of research has largely focused on the acute management of MSF, particularly the use of doxycycline as the first-line treatment. Doxycycline is highly effective against Rickettsia species and is widely used due to its ability to penetrate intracellularly, where the bacteria reside[10]. However, the literature is sparse regarding the long-term health outcomes of MSF, with most studies concentrating on immediate treatment outcomes rather than the prolonged effects of the disease itself[11,12]. This lack of data is particularly problematic for pediatric patients, who may experience different long-term outcomes compared to adults due to their developing physiology and immune systems.

Given the limited research on the chronic effects of MSF, particularly in children, there is a critical need for studies that investigate the long-term health consequences of the disease. Understanding these outcomes is essential for developing comprehensive management strategies that extend beyond the acute phase of the illness and for improving long-term care protocols[13,14]. The potential for MSF to cause lasting health issues underscores the importance of monitoring patients well after the resolution of acute symptoms, especially in regions like Al-Karak, where the disease is endemic.

This study aims to address this significant gap by investigating the long-term health outcomes of children diagnosed with MSF in Karak, Jordan. Unlike previous studies that have primarily focused on the efficacy and safety of doxycycline therapy, this research will concentrate on the chronic effects of the disease itself. The study will explore potential long-term complications such as chronic cardiovascular, neurological, and musculoskeletal conditions, providing much-needed data on the prolonged impact of Rickettsia infections in pediatric populations[15,16].

Specifically, this study will investigate a comprehensive range of long-term outcomes across various systems, including cardiovascular, dermatology, renal, growth, liver, hematologic, musculoskeletal, neurological, respiratory, and gastrointestinal systems. By examining these diverse health aspects, the study aims to provide a holistic understanding of the chronic effects of MSF on pediatric patients, potentially identifying areas of concern that have not been previously documented in the literature[17,18]. This comprehensive approach is expected to yield critical insights that could inform future clinical practices and public health strategies in regions where MSF is endemic.

This work builds on and extends the findings of previous research, such as the "Epidemiological Evaluation of Mediterranean Spotted Fever in Children of the Karak Province in South Jordan," but shifts the focus to long-term outcomes, which have been largely overlooked in the literature[19].

METHODOLOGY

Study Design: This prospective observational study was conducted at the outpatient clinics of Al-Karak Governmental Hospital, located in Al Karak province of Southern Jordan. Serving as a primary Healthcare Facility, the hospital caters to a diverse patient population. Ethical approval for the study was obtained from the institutional review board at Mutah University (reference number: 952023), ensuring adherence to established research guidelines and ethical standards. The study adhered to the ethical principles outlined in the Declaration of Helsinki. The study spanned from January 2013 to December 2022.

Participant Recruitment and Consent: A comprehensive recruitment strategy was employed to identify eligible participants. The study targeted children aged 1 to 15 years who presented with fever, headache, and a characteristic spotted rash suggestive of MSF and confirmed to be caused by Rickettsia conorii. A written informed consent was obtained from each participant or his/her legal guardian after a thorough explanation of the study objectives and procedures.

Inclusion Criteria: They were carefully defined to ensure the selection of participants met the study objectives and criteria for diagnosis and treatment. The enrolled participants in the study were children aged between 1-15 years presenting with fever, headache, and a spotted rash indicative of MSF, patients with MSF admitted to Al-Karak Governmental Hospital outpatient clinics between January 2013 and December 2022 symptoms and treated with a short course of doxycycline therapy during this period, patients with confirmed diagnosis of MSF using an ELISA assay and the participants who provided written informed consent or whose legal guardians provided consent for their participation.

Exclusion Criteria: Patients outside the specified age range of 1-15 years, patients with inconsistent symptoms with MSF, participants who did not provide written informed consent or whose legal guardians did not provide consent to their participation in the study, patients with doxycycline therapy contraindications or other medical conditions necessitating the use of alternative therapy approaches, those who received incomplete or inadequate treatment for MSF and patients with incomplete medical records or insufficient data for analysis were excluded from the study.

Confirmation of Diagnosis and Treatment Protocol: The diagnosis of MSF was confirmed using an ELISA assay with a 96-well plate coated with antigen from the Moroccan strain (ATCC VR-141) of Rickettsia conorii. The treatment protocol in the hospital is dependent on a short course and acute timely management involving oral doxycycline therapy administered at a dosage of 4 mg/kg for ten days or for complete clinical recovery. The decision to initiate doxycycline therapy was carefully considered, balancing the benefits against potential risks, especially the risk of permanent dental discolouration in children under the age of eight years.

Data Collection and Assessment: A structured data collection process was implemented to gather relevant information, including demographics, clinical symptoms, and history of animal contact or insect bites. Detailed patient questionnaires were employed to obtain comprehensive medical histories and assess potential risk factors. Physical examinations were conducted by multidisciplinary teams comprising specialized consultants in Paediatrics, Neonatology, Dentistry, and Dermatology. Laboratory investigations and radiological interventions such as electrocardiograms, echocardiography, abdominal ultrasound, and panoramic dental X-rays, were performed as necessary.

Follow-up and Outcomes Evaluation: Participants underwent systematic follow-up assessments to monitor for any complications associated with Rickettsia conorii infection or doxycycline therapy. The assessed parameters included growth, development, cognitive function, and overall clinical status. Laboratory analyses involved inflammatory markers, complete blood counts, liver enzymes, creatine phosphokinase, creatinine, 25-hydroxy vitamin D, calcium, and electrolytes. Anthropometric parameters, including height, weight percentiles, and Z-scores, were precisely documented and analyzed.

Data Analysis and Interpretation: The appropriate statistical analyses were used for evaluating the clinical post-therapy outcomes, morbidity, and mortality rates. The efficacy and safety of doxycycline therapy in pediatric patients with MSF were critically assessed based on the

collected data, with particular attention to potential adverse effects and long-term implications.

Clinical Data and Follow-up: Clinical data were extracted from the Jordan Center for Disease Control and the Hakeem E-health Program, including patient sex, nationality, residency location, type of housing, age at diagnosis, the date of symptom onset, hospital admission date, checklist of symptoms, and history of animal contact or insect bites. A detailed patient questionnaire for follow-up purposes was completed by the child and parents, if applicable, assisted by two sixth-year medical students. Physical examinations, including vital signs and growth parameters, were performed along with detailed dental and dermatological examinations by specialist consultants. Laboratory tests as well as the necessary radiological interventions were ordered.

Review and Outcome Analysis: Patient clinical notes were reviewed for complications or complaints related to Rickettsia, doxycycline therapy, or other general complaints, with a focus on dermatological issues, growth parameters, developmental milestones, school performance, and cognitive function. Data on medication usage and previous post-Rickettsia diagnosis admissions were collected. Clinical post-doxycycline therapy outcomes, including morbidity and mortality, were assessed. Laboratory data included inflammatory markers, urinalysis, complete blood counts, liver enzymes, creatine phosphokinase, creatinine, 25-hydroxy vitamin D, calcium and electrolytes.

Growth and Development Evaluation: Weight and height were measured at follow-up, and height, weight percentiles, and Z-scores were calculated using the Medscape Calculator. These measurements were used to assess the nutritional and growth status of children and to identify any long-term side effects. Cognitive functions were evaluated based on school performance, reading ability, speech, and mental status.

RESULTS

In this cohort study, 63 patients were initially enrolled. Four patients (6.3%) died during the acute stage. Their death was attributed to the delay in seeking medical assistance and very late admission to the hospitals after the onset of infection, which led to the delayed presentation, diagnosis, and initiation of doxycycline treatment. This resulted in the development of multiorgan failure, primarily acute renal failure, and severe thrombocytopenia. Nine patients were excluded from the study, primarily due to their nomadic lifestyle, as they reside in tents and did not comply with follow-up.

Consequently, 50 cases were included in the long-term follow-up, with 20 patients (40%) females and 30 patients (60%) males among those cured. The overall cure rate was 59 out of 63 patients (93.7%).

The majority of the study population (94%) was admitted to Al-Karak Governmental Teaching Hospital and a small portion (6%) was admitted to Prince Ali Bin Al-Hussien Military Hospital. The nationality distribution was predominantly Jordanian, accounting for 98% of the participants, while only 2% were Yemeni. Regarding living conditions, 94% of the participants resided in urban areas, with the remaining 6% living in rural areas or tents.

Gender distribution showed that 60% of the participants were males, and 40% were females. A significant proportion of the participants had various animal exposures, with 68% reporting contact with sheep. Other animals to which participants were exposed included dogs (14%), cats (10%), horses (4%), chickens (2%), and camels (2%).

Tick exposure was prevalent among the participants, with 80% reporting such an exposure, whereas 20% had no tick exposure. Additionally, most participants (96%) had no known contact with sick patients, while 4% reported such contact.

Notably, none of the participants had travelled, indicating that all cases of Rickettsia conorii infection were locally acquired within this cohort [Table 1].

These results provide a comprehensive snapshot of the health status of the patients, indicating normal ranges for most parameters with some variability. The CBC laboratory results for the 50 patients indicate that the majority had normal blood parameters. Specifically, 92.0%, 98%, 98% and 96% have normal RBCs count, RDW levels, WBCs count, and platelet count, respectively. However, there are some deviations in haemoglobin levels, with 6.0% showing high levels and 8.0% showing low levels. Additionally, 18.0% of patients have low PCV and MCV levels and 6% have low MCH. 92% of the patients have normal ESR levels, with a small portion (8%) exhibiting elevated ESR levels, indicating low levels of inflammation. Similarly, nearly all patients (96%) have normal CRP levels, while only a minor fraction (4%) shows positive CRP levels, suggesting minimal inflammatory activity overall.

All patients in the sample have normal calcium, sodium, and potassium levels, indicating a stable electrolyte balance for these minerals. Nearly all patients (98%) have normal phosphate levels, with a small fraction (2%) showing low phosphate levels. Additionally, all patients have normal glucose levels, suggesting good metabolic control within this group.

In this sample of 50 patients, the biochemical test results reveal that most markers are within normal ranges. All patients have normal levels of total bilirubin, direct bilirubin, serum albumin, serum creatinine, and total protein. This indicates stable liver function, protein synthesis, and kidney function for the entire sample group.

Table 1. Demographic characteristics of the studied sample

Characteristic	Number	%
Hospital admission		
- Al-Karak Governmental Teaching Hospital	47	94
- Prince Ali Bin Al-Hussien Military Hospital.	3	6
Living conditions		
- Urban	47	94
- Rural	3	6
Gender		
- Male	30	60
- Female	20	40
Animal exposure		
- Sheep	34	68
- Dogs	7	14
- Cats	5	10
- Horses	2	4
- Chickens	1	2
- Camels	1	2
Tick exposure		
- Yes	40	80
- No	10	20
Sick patients exposure		
- Yes	48	96
- No	2	4
Acquired infection		
- Abroad	None	0
- Local	50	100

For Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), 98% of the patients have normal levels. However, 4% (2 cases) have slightly elevated AST levels (46 and 48, where the normal range is up to 40), and 2% (1 case) have a minimal increase in ALT levels (48, normal up to 40).

Regarding coagulation parameters, 98% of patients have normal Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) levels, with one case showing elevated PT (16, normal 11 to 14) and INR (1.27) levels. This individual also has a PTT of 38, indicating potential coagulation issues. Urea and serum creatinine levels are normal across the entire sample.

The CPK (Creatine Phosphokinase) levels are notably varied, with 76% (38 cases) showing elevated levels, 4% (2 cases) having low levels, and only 20% within the normal range. This suggests potential muscle damage or stress in a significant portion of the sample.

For Alkaline Phosphatase (ALP) levels, 84% of patients have normal levels, while 16% (8 cases) have low levels, which may require further investigation into possible liver or bone conditions.

Overall, the biochemical test results indicate that while the majority of patients have normal levels for most of the markers, there are specific areas, such as elevated CPK levels, as well as isolated cases of elevated liver enzymes and coagulation markers, that may require further medical attention.

The urine test results for the sample of 50 patients revealed that most have a urine pH of 5 (68%), indicating a slightly acidic environment, with fewer patients having pH levels ranging between 6 and 9. All patients showed negative results for urine glucose, suggesting normal blood glucose levels. One individual exhibited microscopic hematuria and elevated urine WBCs due to a urinary tract infection.

Nearly all patients (98%) have normal levels of ketone bodies and only one patient showed positive results. Mild proteinuria with, plus 1 to 2 was observed in 6% of patients, while the remaining 94% had no protein in their urine. The majority of patients (94%) had amorphous urate crystals in their urine, with a small number (6%) showing calcium oxalate crystals. Most patients (98%) had few urine crystals, with only one patient having many crystals, which may warrant further investigation to prevent potential stone formation [Table 2].

The age stratification of doxycycline exposure in the study population revealed that 90% of the participants were 8 years old or younger, while only 10% were older than 8 years. This indicates a predominant exposure to doxycycline among younger children. The standard dose of doxycycline administered was consistent across participants being 4.0 mg/kg.

Participants received doxycycline for an average duration of 3.4082±0.70 days at home (range: 3 to 5 days) and 7.67±1.62 days in the hospital (range: 6 to 13 days). The total duration of doxycycline therapy averaged 10.20±1.04 days (range: 8 to 13 days). The age at which participants were exposed to doxycycline ranged from 1 to 13 years, with an average age of 5.04±3.72 years. At the time of examination, the participants' ages ranged from 3 to 22 years, with a mean age of 10±3.95 years. The time interval between doxycycline exposure and the follow-up examination varied from 1 to 10 years, averaging 5.09±2.39 years [Table 3].

The clinical evaluation showed that none of the 50 patients enrolled in the study developed any one of the following diseases autoimmune diseases, tuberculosis, chronic lung disease, heart disease, diabetes mellitus, hepatitis and thyroid disease with no incidence of these conditions. Regarding asthma, 94% of participants reported no asthma, while 6% (3 participants) reported having asthma. These results indicate that the occurrence of chronic diseases post-Rickettsia conorii infection in this cohort study was minimal except for asthma which is reported by a small number of participants.

Regarding the reported new complaints of post-Rickettsia conorii infection by patients, 62% reported no new complaints. Among those who did report new issues, the conditions were varied and included abdominal pain (2%), bilateral myringotomy surgery (2%), eczema (2%), encopresis (2%), granulomas annulare (2%), hallucinations (2%), headaches (2%), hypersensitivity airway (2%), knee pain (2%),

Table 2. Laboratory findings in a patient with Mediterranean spotted fever under the short course of doxycycline therapy

Parameter	Minimum	Maximum	Mean ±SD
Haemoglobin	11.20	17.10	13.2324±1.25876
WBC	3.80	14.08	6.9567±2.35532
PLT	169.00	513.00	313.00±74.17470
ESR	5.00	62.00	18.5172±14.36171
Na	134.00	145.00	138.9048±2.96162
Glucose	73.10	141.90	87.9925±11.74803
AST	13.90	46.20	27.5452±7.06124
ALT	7.40	48.80	14.9488±6.91528
Total bilirubin	.12	.910	.3514±0.203810
Direct bilirubin	.06	.330	.1332±0.065590
PT	10.50	31.00	14.2816±4.46342
PTT	13.00	38.30	30.9767±5.41866
INR	0.90	10.00	1.3340±1.60986

Table 3. Treatment and outcomes

The age stratification of doxycycline exposure	8 years or younger	Older than 8 years
(standard dose of doxycycline 4mg/kg)	45 patients (90%)	5 patients (10%)
Average duration of doxycycline therapy	At home	In the hospital
	3-5 days	6-13 days
	Mean±SD=3.4082±0.7 days	Mean±SD=7.67±1.62days
Total duration of doxycycline therapy	8-13 days	
	Mean±SD=10.2±1.04 days	
Age of the patient at the time of examination when exposed to doxycycline	1 to 13 years,	
	Mean±SD=5.04±3.72 years	
Age of patients at the time of examination	3 to 22 years	
	Mean±SD=10.0±3.95 years	
The time interval between doxycycline exposure and the follow-up examination	1 to 10 years	
	Mean±SD=5.09±2.39 years	

leg pain and edema (2%), lymphadenopathy (2%), myopia (4%), otitis media (6%), shoulder dislocation (2%), and tonsillitis (6%). These findings suggest that the new complaints observed were diverse and do not appear to be directly related to complications from Rickettsia conorii infection.

The vital signs of all participants were evaluated to ensure the normal ranges for their age groups. All 50 patients (100%) had normal heart rates, respiratory rates, oxygen saturation levels, and body temperatures during the follow-up period. These findings confirm that all patients maintained normal consistent vital signs during the follow-up period.

The general appearance and symptoms of the group of patients reveal that the vast majority did not exhibit jaundice (98%) or cyanosis (100%). Pallor was uncommon, affecting only 4% of participants. Ear pain was experienced by 8%, while recurrent fever was reported by 12% of participants. Chills were rare, occurring in 4%, and headaches were relatively more common, affecting 26% of participants. Most participants did not have a rash, though 10% did, and 2% had a specific scalp lesion [Table 4].

Table 4. The developed chronic medical conditions, new complaints, vital signs and general appearance of the patients during the follow-up period post-Rickettsia conorii infection

Chronic medical condition	**Number**	**%**
Autoimmune disease	None	0
Tuberculosis	None	0
Asthma		
- Yes	3	6
- No	47	94
Chronic lung disease	None	0
Heart disease	None	0
Diabetes mellitus	None	0
Hepatitis	None	0
Thyroid disease	None	0
New complaints		
abdominal pain	1	2
bilateral myringotomy surgery	1	2
eczema	1	2
encopresis	1	2
granulomas annulare	1	2
hallucinations	1	2
headaches	1	2
hypersensitivity airway	1	2
knee pain	1	2
leg pain and oedema lymphadenopathy	1	2
myopia	2	4
otitis media	3	6
shoulder dislocation	1	2
tonsillitis	3	6
None	3	62
Vital signs		
Heart rate		
- Normal	50	100
- Abnormal	None	0
Respiratory rate		
- Normal	50	100
- Abnormal	None	0
Oxygen saturation level		
- Normal	50	100
- Abnormal	0	0
Body temperature		
- Normal	50	100
- Abnormal	0	0
General Appearance		
Cyanosis		
- Yes	0	0
- No	50	100
Jaundice		
- Yes	1	2
- No	49	98
Pallor		
- Yes	2	4
- No	48	96
Ear pain		
- Yes	4	8
- No	46	92
Recurrent fever		
- Yes	6	12
- No	44	88
Headache		
- Yes	13	26
- No	37	74
Chills		
- Yes	2	4
- No	48	96
Rash		
- Yes	5	10
- No	45	90
Specific scalp lesion		
- Yes	1	2
- No	49	98

Table 5. The interpretation of growth parameters during the follow-up period post-Rickettsia conorii infection and doxycycline therapy

Parameter	**Number**	**%**
Z score/height		
- Normal	44	88
- Stunted	5	10
- Very tall	1	2
Z score/weight		
- Normal	41	82
- Possible growth problems	6	12
- Underweight	1	2
- Severely underweight	2	4
Z score height/weight		
- Normal height/weight ratio	45	90
- Possible risk of overweight	5	10
Height		
- Range	99.00 to 186.00 cm	
- Average	133.67±18.55 cm.	
Weight		
- Range	16.00 to 83.60 kg,	
- Average	32.95±15.56 kg.	
Body mass index		
- Range	12.80 to 27.20	
- Average	17.66±4.45	

The results of evaluating the long-term growth impacts of Rickettsia conorii infection and doxycycline treatment revealed that the height Z scores showed that 88% of the participants had normal height, 10% were stunted, and 2% were very tall. For weight Z scores, 82% had normal weight, 12% showed possible growth problems, 2% were underweight, and 4% were severely underweight. The height/weight Z scores indicated that 90% of the children had normal height-to-weight ratios, while 10% were at a possible risk of being overweight. These results suggest that while the majority of the children maintained normal growth parameters, a notable minority experienced stunting, underweight, or potentially overweight issues.

Further analysis of the growth parameters showed a range in height from 99.00 to 186.00 cm, with an average height of 133.67±18.55 cm. The weight ranged from 16.00 to 83.60 kg, with an average weight of 32.95±15.56 kg. Body Mass Index (BMI) values ranged from 12.80 to 27.20, with a mean of 17.66±4.45. These means and deviations reinforce that most children were within the normal growth range [Table 5].

The results of the examination of the cardiovascular system revealed normal S1 and S2 sounds in all patients, 84% of them had no murmur, a small portion had either ejection systolic or physiological murmurs, 98% had normal ECG and Echo results and one patient showed mild calcification on the aortic valve. None of the 50 examined patients showed signs of arrhythmias or heart block, indicating a 100% absence of these cardiovascular conditions in the group tested.

The majority of the 50 patients did not show significant issues regarding gastrointestinal examination. Only 4% had recurrent abdominal pain and nausea. Anorexia affected 24% of participants, while an increased appetite was very rare (2%). Recurrent vomiting and chronic diarrhoea were reported by 6% of the patients. Hepatomegaly and splenomegaly were notified in only 2% of the patients.

All patients had a normal respiratory examination and did not experience wheezing or sore throat. Chronic coughing was rare, affecting 4% of the patients. Chest pain, nasal congestion, muscle pain, shoulder pain/generalized bone pain, and lymphadenopathy were also relatively uncommon, each one of them is affected between 2% and 6% of patients.

Regarding the neurological examination of all patients, it is indicated that most of them did not show significant neurological abnormalities. Difficulty swallowing, photophobia, cerebellar and vestibular dysfunction, proximal motor weakness, positive Babinski signs, hyperactive reflexes, irritability, dizziness, disorientation, perseveration, gait disturbances, dysarthria, and confusion were absent in all patients. The examination of some patients (2-10%) revealed some neurological conditions such as vestibular dysfunction, deafness, spastic paraparesis, urinary incontinence and retention, numbness and paresthesia, epileptiform attacks, seizures, generalized spasticity, hallucinations, fatigue, lethargy, labile mood, mental retardation, inability to read, reduced attention span, impaired memory and intellectual function, speech delay, and persistently abnormal mental status. 82%, 10%, 4% and 4% of the enrolled patients in the study showed excellent, very good, good and poor school performance levels, respectively.

The specified dermatologic issues such as recurrent superficial scrotal ulceration, petechial eruption, recurrent skin lacerations, decubitus ulcers, acne, pruritus, fixed drug reactions, photo onycholysis, bilateral phototoxic rashes, change in hair colour, or blue subungual discolouration were not detected in most of the examined patients. Only 4% of the patients were found to have ichthyosis and rash, while 2% exhibited photosensitivity, hyperpigmentation, and erythematous rash associated with a second-degree burn (Table 6).

Table 6. The results of the physical examination of different systems, school performance and dermatological assessment during the follow-up period post-Rickettsia conorii infection and doxycycline therapy

System	**Number**	**%**
Cardiovascular system		
1- *S1 and S2 sounds*		
- Normal	50	100
- Abnormal	0	0
2- *Murmur*		
- Yes	8	16
- No	42	84
3**- *ECG and Echo***		
- Normal	49	98
- Calcified aortic valve	1	2
4- Arrhythmias		
- Yes	0	0
- ***No***	50	100
5- Heart block		
- Yes	0	0
- No	50	100
Gastrointestinal system		
1- Recurrent abdominal pain		
- Yes	2	4
- No	48	96
2- Nausea		
- Yes	2	4
- No	48	96
3- Anorexia		
- Yes	12	24
- No	38	76

4- Increased appetite		
- Yes	1	2
- No	49	98
5- Recurrent vomiting		
- Yes	3	6
- No	47	94
6- Hepatomegaly and splenomegaly		
- Yes	1	2
- No	49	98
Respiratory system		
1- Chronic coughing	2	4
- Yes	48	96
- No		
2- Chest pain, nasal congestion, muscle pain, shoulder pain/generalized bone pain, and lymphadenopathy		
- Yes	3	6
- No	47	94
Nervous system		
1- Difficulty swallowing, photophobia, cerebellar and vestibular dysfunction, proximal motor weakness, positive Babinski signs, hyperactive reflexes, irritability, dizziness, disorientation, perseveration, gait disturbances, dysarthria, and confusion		
- Yes	0	0
- No	50	100
2- Vestibular dysfunction, deafness, spastic paraparesis, urinary incontinence and retention, numbness and paresthesia, epileptiform attacks, seizures, generalized spasticity, hallucinations, fatigue, lethargy, labile mood, mental retardation, inability to read, reduced attention span, impaired memory and intellectual function, speech delay, and persistently abnormal mental status		
- Yes	5	10
- No	45	90
School performance levels		
- Excellent	41	82
- Very good	5	10
- Good	2	4
- Poor	2	4
Dermatologic assessment		
1- Recurrent superficial scrotal ulceration, petechial eruption, recurrent skin lacerations, decubitus ulcers, acne, pruritus, fixed drug reactions, photo onycholysis, bilateral phototoxic rashes, change in hair colour, or blue subungual discolouration.		
- Yes	0	0
- No	50	100
2- Ichthyosis and rash		
- Yes	2	4
- No	48	96
3- Photosensitivity, hyperpigmentation,and erythematous rash associated with a second-degree burn		
- Yes	1	2
- No	49	48

DISCUSSION

MSF is mostly a tick-borne infection caused by R. conorii, endemic to the countries along the Mediterranean Sea coast, North Africa, Southern Europe, and India. However, as a result of the growth of tourism, some MSF cases are imported to non-endemic regions and countries[20]. MSF shows typical and atypical symptoms including fever, maculopapular rash, and especially the characteristic eschar (“tache noire”), also, severe multi-organ complications may also exist[21].

Since there are no vaccines for MSF, doxycycline remains the drug of choice, doxycycline given for the treatment of MSF even in severe cases and elderly patients in a single day is an efficient treatment because it reduces the symptoms duration and prevents the progression of the disease to the very serious form[22]. Doxycycline therapy is cost-effective and well tolerated because of the short course regimen and in case of admission of the patient to ICU, it is advised to continue doxycycline therapy till the achievement of the clinical improvement. The effect of doxycycline therapy for treating cases of MSF was shown that it is an effective and safe treatment in adults and children, 3- 3-day doxycycline therapy is effective[23]. A single doxycycline dose (200 mg) was to be adequate for the treatment of MSF. However, in the atypical forms of disease, there is a debate about using short-course therapy[24]. In the presence of laboratory findings of MSF along with skin lesions such as maculopapular rash, the outcomes can be favorable without any complications when the administration of doxycycline started as the first line of treatment and the rapid response to the therapy could be beneficial in the differential diagnosis of the disease in case of diagnosis suspicion[20,25].

In the in vitro and in vivo study[26], it was revealed that short-term doxycycline therapy is highly efficient for treating rickettsiosis. Clinical studies have confirmed that doxycycline shortens MSF course and induces symptoms of rapid remission[27].

The results of the present study clarify that the demographic insights underscore the significant effect of animal and tick exposure in the study population and suggest that Rickettsia conorii infection is a local issue, not influenced by travel. Overall, the results indicate generally normal urine composition with some isolated cases of proteinuria, crystal formation, and urinary tract infection.

Additionally, our findings of doxycycline therapy emphasize that doxycycline was primarily administered to younger children. The duration of doxycycline treatment extended beyond a week, with notable variation in home and hospital settings. The follow-up examinations of the patients occurred several years post-doxycycline therapy, providing a substantial interval to assess long-term outcomes. The data of the chronic medical conditions post-doxycycline therapy indicate that patients mostly showed no significant abnormalities in general appearance and only a small portion of the patients experienced specific symptoms. Regarding the physical examinations following doxycycline therapy, our results indicate no significant abnormalities in general appearance in most of the examined patients, and specific symptoms were experienced by only a few numbers of them.

Our study evaluated the long-term growth impacts of Rickettsia conorii infection and doxycycline treatment in children, focusing on stunting, wasting, underweight rates, and the risk of being overweight. The findings revealed that 10% of the participants were stunted, 4% were wasted, 2% were underweight, and 12% were at risk of being overweight. Additionally, 94% of the participants were from tents and rural areas, while 6% were from suburban areas.

When compared to national data from 2012 for Jordanian pediatric populations, which reported stunting, wasting, and underweight rates among children under 5 years at 7.7%, 2.4%, and 3%, respectively, several observations can be made[28]. Our study identified a stunting rate of 10%, which is slightly higher than the national average of 7.7%. This suggests that children who experienced Rickettsia conorii infection and doxycycline treatment may have a marginally increased risk of stunting. However, this rate is still within a comparable range of the general pediatric population in Jordan.

The national data indicated a wasting rate of 2.4%, whereas our study found a slightly higher rate of 4%[28]. This suggests a potential impact of the infection and treatment on wasting, though the rate is still relatively close to the national average. Additionally, our study found an underweight rate of 2%, which is slightly lower than the national average of 3%[28]. This indicates that, despite the infection and treatment, the underweight rates among our participants are slightly better than the national average.

Our study found that 12% of the children were at risk of being overweight, a concern not directly addressed in the national data. This finding underscores the need for balanced nutritional interventions and monitoring to prevent potential overweight issues in this population. Despite these differences, it is important to highlight that the majority of the children in our study maintained normal growth parameters, indicating that the impact of the infection and treatment may not be significantly different from the general population.

A previous study conducted in Jordan on pediatric growth patterns showed similar issues with short stature and weight abnormalities. The study reported prevalence rates of 4.9% of short stature, 5.7% of underweight, 17.3% of overweight, and 15.7% of obesity, with variations between rural and urban regions[29]. Short stature and underweight were more dominant in rural regions, while obesity was higher in urban regions[29].

A recent study also found significant deviations in the measurements of Jordanian children from international growth standards, suggesting the need for Jordanian-specific growth standards to enhance the accuracy of monitoring and evaluating children's health[30]. The better socioeconomic status in urban regions plays a vital role in achieving better growth parameters compared to rural regions[31]. This urban-rural socioeconomic status difference may explain some of the growth outcome variations observed in different regions of Jordan[30-32].

In our study, 94% of the participants were from tents and rural areas, and 6% were from suburban areas. This rural predominance could influence the growth outcomes observed, as rural regions generally have less access to healthcare, nutrition, and socioeconomic conditions, which can negatively affect growth parameters.

In conclusion, while our study shows that the incidences of stunting, wasting, and underweight are slightly different from the national averages for Jordanian pediatric populations, they still align reasonably well. The higher risk of overweight observed in our study highlights the need for targeted interventions. Further research is warranted to understand the long-term impacts of Rickettsia conorii infection and doxycycline treatment on child growth and development. This will help in formulating effective health policies and treatment protocols to mitigate any adverse growth outcomes in affected children.

The results of the interpretation strengthen that most children were within the normal growth range. A previous study conducted for evaluating pediatric growth in Jordan stated a relevant standard for the growth pattern, it was shown that the growth and development of Jordanian children explored similar issues with short stature and weight abnormalities, however, the prevalence rates were variable, the study showed 4.9 %, 5.7 %, 17.3 %, and 15.7% prevalence rates for short stature, underweight, overweight, and obesity, respectively. Short stature and underweight were more dominant in the rural regions compared to the urban ones, while obesity was higher in the urban regions of Jordan[33]. A recent study found significant deviations in the measurements of Jordanian children from reference values of the international standards and growth, this is why the Jordanian-specific growth standard is highly suggested for enhancing the accuracy in monitoring and evaluating children's healthy lives. The best socioeconomic status in urban regions plays a vital role for the children in getting better growth parameters compared to the children in rural regions[34]. This urban-rural socioeconomic status comparable difference may explain some of the growth outcomes variations observed in different regions of Jordan.

Regarding the physical examination of body systems post-doxycycline therapy, the findings of cardiovascular system examination were no murmur, mostly no ECG and Echo abnormalities except for a case of mild aortic valve calcification, no arrhythmias and no heart block. The examination of the gastrointestinal system showed that 24% of the examined patients were affected by anorexia, 6% reported vomiting and chronic diarrhoea, hepato-splenomegaly was detected only in one patient, and overall, most of the participated patients did not exhibit major gastrointestinal abnormalities, with only a few experiencing specific symptoms. For the respiratory system, almost all patients had normal findings except one to three of them suffering from chest pain, lymphadenopathy and nasal congestion but, overall, no significant respiratory abnormalities were reported. Generally, the neurological examination did not show significant symptoms, except for one to five patients experiencing deafness, urinary incontinence and retention, spasticity, hallucinations, fatigue and mental retardation, our findings propose predominant neurological status almost for all patients. The majority of patients performed in the schools during

the post-doxycycline period at an excellent level, while the lowest percentage was for the poor and the good school performance levels. The dermatological assessment revealed that the majority of examined patients did not show any of the specified conditions. Generally, the prevalence of some conditions such as ichthyosis, rash, photosensitivity, hyperpigmentation, and erythematous rash was very low among the assessed patients.

The limitations of the present study include the small sample size, no control group, any biases in data collection, and the enrolled patients were only from the southern region of Jordan.

CONCLUSIONS

The study concludes with an evaluation of the long-term health outcomes of children post-doxycycline therapy of MSF, the obtained results showed that most of the included patients have normal levels for most of the studied parameters, the development of chronic diseases, the occurrence of new complaints and even the changes in the general appearance during doxycycline therapy are very minimal, these means and standard deviations of the growth parameters of the patients were within normal growth range. Upon the examination of body systems, the results showed very limited specified abnormalities such as murmurs, anorexia, recurrent vomiting and chronic diarrhoea, muscle pain, lymphadenopathy, deafness, spastic paraparesis, generalized spasticity, hallucinations, fatigue, lethargy, mental retardation, ichthyosis and rash. While the school performance level was excellent in most of the patients. For future research, the evaluation of long-term health outcomes post-doxycycline therapy of MSF should include the severity of the disease and the laboratory trials to get a vaccine against the disease.

Authorship Contribution: Amjad Tarawneh: He contributed to the study by formulating and evolving the overarching research goals and aims (Conceptualisation). He developed the study methodology and created models (Methodology), and conducted the research and investigation process, specifically performing data collection (Investigation). He applied statistical and computational techniques to analyse the study data (Formal analysis), provided study materials and analysis tools (Resources), and managed data annotation and maintenance for initial use and later reuse (Data Curation). Amjad also prepared and wrote the initial draft of the manuscript (Writing - Original Draft), critically reviewed, commented on, and revised the manuscript (Writing - Review & Editing), and oversaw and led the planning and execution of the research activity (Supervision). Additionally, he managed and coordinated the research activity planning and execution (Project administration). **Maryam I. Abutouq:** She contributed to the study by formulating the research goals and methodology, conducting data collection, applying statistical analysis, managing data curation, and writing the initial proposal. **Sondos Al-abbadi:** She contributed to the study by formulating the research goals and methodology, conducting data collection, applying statistical analysis, managing data curation, and writing the initial proposal. **Awad Tarawneh:** He contributed to the study by formulating the research goals and methodology, conducting data collection, applying statistical analysis, managing data curation, and writing the initial proposal. **Ansam Atrooz:** She contributed to the study by formulating the research goals and methodology, conducting data collection, applying statistical analysis, managing data curation, and writing the initial proposal.

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