

# Mediterranean Spotted Fever in Children: Study of a Portuguese Endemic Region

## Febre Escaro-Nodular na Criança: Aspectos Epidemiológicos e Clínicos Numa Região Endêmica em Portugal



Sara PEIXOTO<sup>1</sup>, Jorge FERREIRA<sup>1</sup>, Joana CARVALHO<sup>1</sup>, Vânia MARTINS<sup>1</sup>  
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### ABSTRACT

**Introduction:** Mediterranean spotted fever is an infectious disease included in the human rickettsiosis group, with its main distribution in the Mediterranean and South European countries. It is an endemic disease in Portugal, with dogs acting as the main domestic reservoir. Children are a particularly vulnerable group due to their close contact with household animals and by frequently playing outdoors. In this study, we aim to describe the local epidemiology and characterize the clinical features and treatment options in a Portuguese endemic region.

**Materials and Methods:** We performed a prospective descriptive study of the Mediterranean spotted fever cases admitted to the paediatrics emergency department of a group II hospital, between January 1<sup>st</sup> 2013 and December 31<sup>st</sup> 2015. All patients were examined by a physician, who was later asked to fill out a detailed questionnaire regarding clinical presentation, diagnostic attitudes and treatment of their patients. Parents were later interviewed and questioned about post-discharge disease evolution.

**Results:** We registered 32 cases (93.9% reported between July and October). After fever, the most frequent reported symptoms were myalgia (37.5%), abdominal pain (25%) and headache (25%). Exanthema was present in 84.4% of cases by the third day of fever: maculonodular (53.1%), papular (37.5%) and macular (9.4%). Eschars were found in 59% of patients, with regional lymphadenopathy present in 46.9% of cases. Azithromycin (84.4%) and doxycycline (15.5%) were the selected treatments in our population, with no cases of therapeutic failure or side-effects reported.

**Conclusion:** The incidence of Mediterranean spotted fever is higher in our population in comparison with the rest of the country. Fever, myalgia, abdominal pain and headache were the most common presenting symptoms, while exanthema was the predominant cutaneous finding. Azithromycin was the preferred treatment and it proved to be successful and safe in all cases.

**Keywords:** Boutonneuse Fever; Child; Exanthema; Portugal; Rickettsia

### RESUMO

**Introdução:** A febre escaro-nodular é uma doença infecciosa aguda incluída no grupo das rickettsioses humanas, que atinge sobretudo os países da bacia do Mediterrâneo e sul da Europa. É uma doença endêmica em Portugal com o cão como principal reservatório doméstico. As crianças são um grupo particularmente vulnerável devido ao contato próximo com animais domésticos e a brincarem em campos e jardins. O principal objetivo deste estudo foi perceber e estudar a epidemiologia local, bem como caracterizar a clínica e a resposta terapêutica da nossa população.

**Materiais e Métodos:** Foi realizado um estudo prospetivo descritivo de todas as crianças com febre escaro-nodular admitidas no serviço de urgência de um hospital grupo II, entre janeiro de 2013 e dezembro de 2015. Todos os doentes foram avaliados por médico, que respondeu a um questionário referente as manifestações clínicas apresentadas e atitudes de diagnóstico e terapêuticas instituídas. Os pais foram posteriormente contactados, por telefone, e questionados sobre a evolução da doença.

**Resultados:** Foram registados 32 casos (93,9% de julho a outubro). Além da febre, as queixas mais frequentes foram mialgias (37,5%), dor abdominal e cefaleias (25%). O exantema estava presente no terceiro dia de febre em 84,4%: maculopapulonodular (53,1%); papular (37,5%) e macular (9,4%). Foi identificada escara em 59% e adenopatia satélite em 46,9%. Azitromicina (84,4%) ou doxiciclina (15,5%) foram os antibióticos de escolha, com sucesso em qualquer dos casos. Não foram relatadas complicações.

**Conclusão:** A incidência de febre escaro-nodular na nossa população é alta, quando comparada com a incidência no restante país. Febre, mialgias e cefaleias foram os principais sintomas e sinais registados enquanto a presença de exantema foi o achado dermatológico predominante. Azitromicina, antibiótico de escolha na maioria dos casos, mostrou ser eficaz.

**Palavras-chave:** Criança; Exantema; Febre Escaro-Nodular; Portugal; Rickettsia

### INTRODUCTION

*Rickettsiae* of the spotted fever group cause human disease all around the world and approximately one-half of the known species of *rickettsiae* can cause human disease, with the remaining organisms acting as non-pathogenic parasites of arthropods. Mediterranean spotted fever (MSF), also known as boutonniere fever, is caused

by *R. conorii* that exists in countries and regions adjacent to the Mediterranean Sea. In Europe, it is endemic in the Mediterranean area, with most cases occurring in summer time, when the tick vectors are highly active. Some European studies have reported a higher incidence rates for infection in recent years, perhaps due to the changes in

<sup>1</sup>. Pediatric Department. Centro Hospitalar de Trás-os-Montes e Alto Douro. Vila Real. Portugal.

✉ Autor correspondente: Sara Peixoto. [saracpeixoto@gmail.com](mailto:saracpeixoto@gmail.com)

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*R. conorii* antigenicity that may be the cause of an acquired higher pathogenicity of this parasite.<sup>1</sup>

MSF was first described in 1910 as a disease that caused high fever and spots.<sup>2</sup> It is transmitted by the dog tick *Rhipicephalus sanguineus*. The tick bite causes a characteristic rash and a distinct mark (*tache noire* or black spot) at the site of the bite. Children are a particularly vulnerable group due to their close contact with household animals and by playing outdoors. MSF is usually a mild disease, but severe complications including hepatic, renal, cardiac, neurological and multiorgan involvement can occur in about 6% – 10% of cases, often the result of a delayed

diagnosis.<sup>3,4</sup> The mortality rate is estimated at around 2.5%.<sup>2</sup>

In Portugal, MSF is an endemic disease, and according to the Directorate-General of Health registers, the number of reported cases has been decreasing over the last few years, with 553 cases of MSF occurring in Portugal between 2011 and 2014 (Figs. 1 and 2), contrary to what has been observed in other countries.<sup>1</sup> Thirty-one cases were reported in Trás-os-Montes region and 51 cases in the Douro region (the regions comprising our catchment area). Despite the mandatory notification of all cases of MSF at a national level, the real incidence of the disease remains unknown.

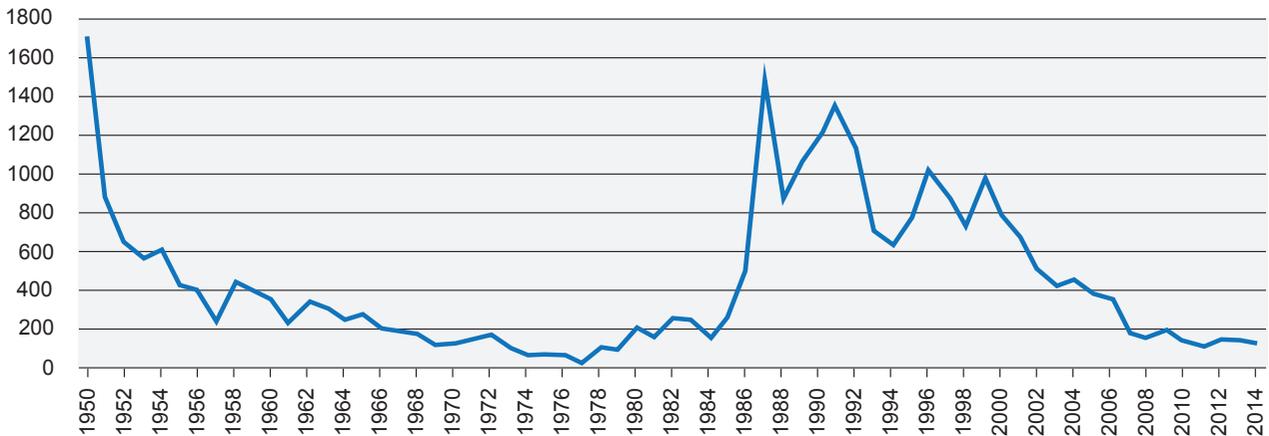


Figure 1 – Number of reported cases of Mediterranean spotted fever in Portugal, 1950 - 2014

Source: Portuguese Directorate General for Health's registers

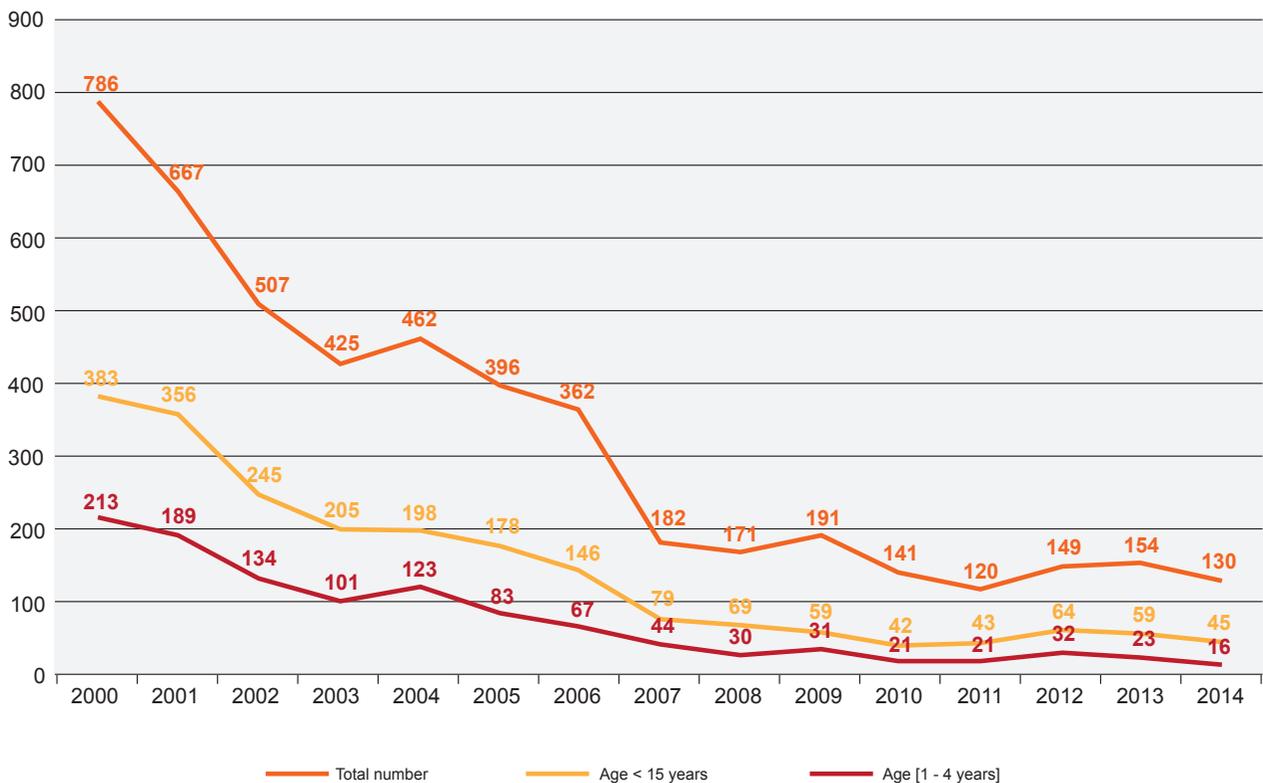


Figure 2 – Total number of reported cases of Mediterranean spotted fever in Portugal, 2000 - 2014 and number of children with < 15-years-old and from 1 to 4-years-old

Source: Portuguese Directorate General for Health's registers

With this study, the authors aim to describe the local epidemiology and to and characterize the clinical features and treatment options in a level II hospital of the north of the country. This study also aims to present the current practices of our department, located in a region with a high incidence of MSD, which we hope may aid to a prompter diagnosis in non-endemic regions and potentially help prevent serious complications.

## MATERIALS AND METHODS

We performed a prospective descriptive study of all MSF cases admitted to our pediatric emergency department, between January 1<sup>st</sup> 2013 and December 31<sup>st</sup> 2015. All patients were examined by a physician and afterwards a detailed open questionnaire was filled out regarding the nature, length and severity of the clinical manifestations

observed. The child's age, gender, clinical presentation, type of rash, presence or absence of eschar and its location, presence of regional lymphadenopathy and its location, contact with animals and antibiotic prescribed were recorded. The diagnosis of MSF was based upon clinical features as defined by the presence of a characteristic rash in a febrile patient plus epidemiologic clues. Upon diagnosis, clinical data was registered by the attending paediatrician and parents were later interviewed (phone-call), for follow-up clinical information. Demographics, clinical presentation, orientation and follow-up were analysed.

Guardians gave informed consent and were assured of the anonymity of the data.

Statistical analyses were performed using SPSS version 24.0 for Windows. The normality of the variable 'age' was assessed using a Kolmogorov-Smirnov test. A student *t*-test

Table 1 – Characterization of the sample (n = 32)

Age (years)	n	(%)	Gender	n	(%)
[0 - 1[	1	(3)	Male	19	(59.4)
[1 - 6[	18	(56.3)	Female	13	(40.6)
[6 - 10[	10	(31.3)			
[10-15]	3	(9.4)			
<b>Mean ± SD: 5.15 ± 3.23</b>					
<b>Median: 4.25</b>					
<b>Min-Máx: 6m - 15A</b>					
Clinic presentation	n	(%)		n	(%)
Myalgia	12	(37.5)	Arthralgia	3	(9.4)
Abdominal pain	8	(25)	Diarrhea	3	(9.4)
Headache	8	(25)	Photophobia	1	(3.1)
Nausea	7	(21.9)			
Rash	n	(%)		n	(%)
Maculonodular	17	(53.1)	Petechial/vasculitis	2	(6.3)
Maculopapular	12	(37.5)	Papulovesicular/vesicula	0	(0)
Macular	3	(9.4)			
Palms and soles of the feet	31	(96.9)			
Eschar n = 19 (59.4%)	n	(%)		n	(%)
Scalp	7	(36.8)	Back	2	(10.5)
Retroauricular	5	(26.3)	Genital	1	(5.3)
Armpit	3	(15.8)	Knee	1	(5.3)
Regional lymphadenopathy n = 15 (46.9%)	n	(%)		n	(%)
Cervical	8	(53.3)	Axillary	1	(6.7)
Occipital	3	(20)	Supraclavicular	1	(6.7)
Retroauricular	2	(13.3)			
Domestic animal n = 26 (81.3%)	n	(%)			
Dog	25	(96.2)			
Cat	1	(3.8)			
Antibiotic	n	(%)			
Doxycycline	5	(15.6)			
Azithromycin	27	(84.4)			

was performed to assess if a significant difference existed between ages, matched by gender and group, treated with azithromycin versus doxycycline. A Mann-Whitney U test was also applied to assess whether a difference existed between the number of days of fever after starting antibiotics. *P* values of less than 0.05 were considered significant.

## RESULTS

We registered 32 cases of MSF: 19 (59.4%) males and 13 (40.6%) females. The characterization of our sample is presented in Table 1. Sample's age average of  $5.2 \pm 3.23$  years old. No statistically differences were found between ages by gender (male  $5.3 \pm 3.6$  years and female  $4.96 \pm 2.7$  years),  $t(30) = 0.286$ ;  $p = 0.777$ .

The majority of cases was reported in Summer months, between July and October (93.9%) (Fig. 3). The first clinical examination occurred during the first three days of disease in 65.6% of our patients. The most frequent reported symptoms were myalgia (37.5%), abdominal pain (25%) and headache (25%). Exanthema was present by the 3<sup>rd</sup> day of fever in 84.4%: maculonodular (53.1%), papular (37.5%) and macular (9.4%) (Fig. 4). Eschars were found in 59% of patients and regional lymphadenopathy in 46.9%. Most children (75%) owned a domestic animal. The antibiotic of choice was doxycycline in five children (15.6%) and azithromycin in 27 (84.4%). No significant statistical difference was found between ages concerning the groups treated with azithromycin *versus* doxycycline ( $4.86 \pm 2.69$  years vs  $6.78 \pm 2.46$ ),  $t(30) = -1.227$ ;  $p = 0.229$ . We carried out the Mann-Whitney U test and found no statistically significant differences in the number of days with fever after starting antibiotic between groups (median of two days in both groups) ( $U = 47.5$ ;  $p = 0.1$ ). No side-effects or complications were reported in our sample.

## DISCUSSION

Our sample illustrates the high incidence of this disease in our catchment area - 32 cases in three years (about 0.21/1000 inhabitants/year) – although it represents only a small part of the cases diagnosed in our country.

The age group ranging from 1 to 4 years of age was the most affected, with no statistically significant differences by gender. We registered an average age of  $5.2 \pm 3.23$  years

old in our sample, similar to reports from other countries, namely  $5.6 \pm 3.12$  years in Sicilian children and  $6 \pm 3.5$  years in children of the Karak province in south Jordan.<sup>1,5</sup>

All patients presented with fever and a rash, similarly to what is frequently described in the literature.<sup>6,7</sup> Headache, classically reported as a symptom, occurred in only 25% of our patients, possibly reflecting under-reporting due to the frequent administration of antipyretics/analgesics for fever. Flu-like symptoms are also common, and in our study, myalgia and abdominal pain were the most frequently described. In two large series of MSF,<sup>5,7</sup> rash was present in 94.5% - 100% of patients and, in our sample, it was found in all cases as described by Pishmisheva *et al* in South Bulgaria.<sup>7</sup> Only 7 (21.9%) of our cases presented with rash in the first day of fever, with the majority (62.5%) appearing on the second and third days of fever. In our sample, the rash was most often maculonodular and only two (6.2%) cases had petechial rash. Some series refer associated petechial rash in approximately 10% of cases.<sup>8</sup>

Many patients with MSF have an eschar or black necrotic scabbed lesion (*tache noire*) at the site of the inoculating tick bite. In our sample 59.4% of patients presented with an eschar, a slightly lower frequency than that described in other series (approximately 70% of patients in two large series),<sup>8,9</sup> but higher than that described by Vitaliti G *et al* (29.09%).<sup>1</sup> This difference can be explained by the evidence that the most frequent strains in Portugal are *Rickettsia conorii* Malish and Israeli tick typhus, in which eschar may occur more rarely.<sup>10</sup> The most frequent inoculation sites found in our sample, included the scalp and the retroauricular region (37.5%), in line with the literature.<sup>10</sup>

As expected, most cases in our series occurred during summer months, namely from July to October (Fig. 3), when the tick vectors are highly active.<sup>5</sup>

Although MSF is typically a benign and self-limited disease in children, early antibiotic treatment reduces the duration of fever and other symptoms and also prevents severe complications. Doxycycline is the usual first line treatment for all patients. However, it is an unpractical drug to prescribe in the paediatric population due to its need for an expensive galenic preparation. Although some studies show better efficacy and safety of doxycycline when compared to macrolides, azithromycin also seems to be an effective and safe alternative in children. In our sample,

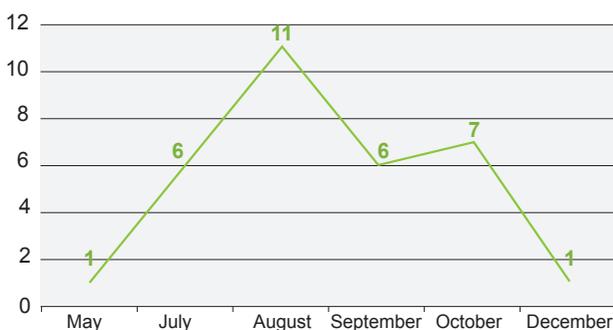


Figure 3 – Diagnosis distribution by months

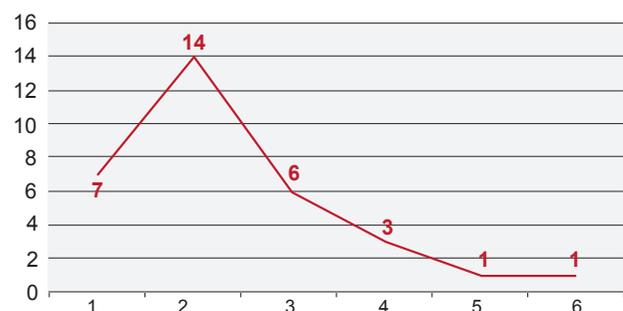


Figure 4 – Distribution of rash by day of fever

84.4% of the children were treated with azithromycin with improvement at follow-up evaluation - resolution of fever after two days of antibiotic therapy- similarly to those treated with doxycycline. In fact, we found no statistically significant difference between the two groups of children, regarding symptom resolution. However, due to our small sample size, we cannot establish a robust comparison between the efficacy of the two therapeutic options.

No complications were reported in our study, probably because usually milder forms of the disease occur in children, while complications of MSF are more commonly seen in patients with underlying disease or the elderly.<sup>11,12</sup>

Our study has some limitations that must be considered. Firstly, we may have underestimated the real burden of MSF in our region, as we only included cases of MSF admitted to our paediatric emergency department (more cases may have been observed in primary health care units or other hospitals in the region). Consequently, disease notification by physicians is mandatory for a correct epidemiologic surveillance, allowing the adoption of preventive measures. Secondly, our study lacks data regarding laboratory test results for MSF diagnosis. In fact, all cases had a clinical diagnosis, based on signs/symptoms (fever, characteristic rash and eschar) and epidemiological criteria (time of year, contact with animals and outdoor activities). Moreover, laboratory investigation, although useful for confirming the diagnosis, is not commonly used in our clinical practice due to the difficulty of obtaining those tests in our hospital and also because they should not be considered relevant if children present good clinical response to treatment.

The number of children treated with doxycycline in our study was limited (n = 5), not allowing a significant comparison with children treated with azithromycin. Post-discharge and follow-up interviews were mostly performed by phone-call, often a few days after complete symptom resolution, which could have interfered with parents' answers and the accuracy of the exact number of days of disease.

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## CONCLUSION

This study investigated and characterized MSF in a population of the north region of Portugal. We believe this will promote awareness for this disease, hopefully leading to an earlier diagnosis and suitable and timely treatment. In our study, we noted a good clinical evolution in all children treated with azithromycin, which is not the first line recommended treatment, but may be an excellent choice for very young children, mainly in economically disadvantaged areas, where the purchase of the galenic formulation may lead to an inadequate therapeutic adherence.

This is a clinically relevant study that reports a higher incidence of this pathology. It also contributes to the active monitoring of current practice in our area, where disease is endemic, allowing further discussion of clinical practices.

## OBSERVATIONS

This work was publicly presented at the 34<sup>th</sup> Annual Meeting of the European Society for Paediatric Infectious Diseases, ESPID 2016, in Brighton, UK, from 10-14 May, 2016.

## PROTECTION OF HUMAN AND ANIMAL SUBJECTS

The authors declare that the research procedures were performed according to the regulations of the institution's ethics committee and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

## CONFIDENTIALITY OF DATA

The authors declare that they have followed the protocols of their work centre regarding the publication of data from patients.

## CONFLICT OF INTEREST

No conflict of interest has been declared by any author.

## FUNDING

No financial support was received by any author.