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Incidence of Mediterranean Spotted Fever in Sicilian children: a clinical-epidemiological observational retrospective study from 1987 to 2010

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SUMMARY

Background: Zoonoses are human infectious diseases caused by pathogens that primarily infect animals. Mediterranean Spotted Fever (MSF) represents one such example, affecting the Mediterranean region, in which household animals can be immune-carriers of infected ticks.

Materials and methods: We retrospectively analysed the incidence and the clinical and laboratory features of MSF caused by *R.Conorii* in children admitted to the Paediatric Operative Unit from 1987 to 2010, for persistent fever and generalised macular-popular erythematous lesions.

Clinical, immunological and serological parameters of 55 cases of Rickettsia infections observed in children between 2 and 11 years of age were collected.

Results: We found an increasing incidence of MSF in childhood from 1987 to 2010. Diagnosis of MSF at the moment of hospital admission was done in 16 patients (29.09%). The presence of the typical Tache noire was observed in 16 cases out of 55 patients (29.09% of cases).

We noticed a different representation of *R. conorii* antigens in serological testing over the time period of the study, corresponding to overall higher incidence rates for infection in the latter years. We also observed a higher incidence of infection in those years in which all four antigens were found positive at serum testing with respect to those years in which only two of the four antigens were observed (1987-1990: 0-16%; 2007-2010: 0.46%; $P<0.005$).

Conclusions: These changes in *R. conorii* antigenicity may be the cause of higher pathogenicity in this parasite, perhaps linked to increased immigration along with consequent changes in the epidemiology of infectious diseases in host countries.

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1. Introduction

Zoonoses are human infectious diseases caused by pathogens that primarily infect animals, with examples including Brucellosis, Tetanus, Toxoplasmosis, Leptospirosis, Rickettsiosis, Echinococcosis, Teniasis).[1] It is important to conduct epidemiologic studies of these infectious diseases, recording up-to-date data to inform prevention measures adopted in every region, including vaccine- and serum-prophylaxis as well as environmental reclamation, since their incidence is still elevated in rural areas such as Sicily and Sardinia.[1–3]

Mediterranean Fevers, usually caused by Rickettsia microorganisms, represent a diagnostic challenge, often with delayed diagnosis with respect to the onset of the disease itself. Mediterranean Fever is an interesting topic of research in areas with a high rural density, such as the Mediterranean areas, in which household animals can be immune carriers of infected ticks.[1,2]

Data from the Italian National Statistic Institute (ISTAT) show that of 1489 cases of Mediterranean fever, 569 (33%) have been diagnosed in Sicily and 333 (22%) in Sardinia.[3] Nevertheless, these data are a likely underestimate because most cases are not

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reported to the relevant authorities and have been treated in regional paediatric hospitals, with a relatively higher risk of severe complications.[4]

Rickettsial infections include a range of microorganisms of the Rickettsia family. These are considered obligate intracellular parasites able to multiply in one or more species of arthropods and can affect both animals and humans. They are divided into the following subgroups.[5,6]:

- Rickettsia of the typhus fever group: murine typhus (*R. mooseri*) and epidemic typhus (*R. prowazekii*), respectively transmitted by fleas and lice; they affect a widespread geographical distribution with infection linked to the presence of rats for *R. mooseri*, and lack of social hygiene for *R. prowazekii.*
- Rickettsia causing spotted fevers: Rocky Mountain spotted fever (RMSF) (*R. rickettsii*) and Mediterranean spotted fever (MSF) (*R. conori*) transmitted by ticks; *R. rickettsii* is prevalent in United States of America, while *R. conori* is widespread in the Mediterranean area, Africa and India.

Rickettsioses are considered benign infectious diseases, although 10% of patients can develop severe complications. The RMSF and the MSF usually cause endothelial damage, leading to coagulation abnormalities from platelet deprivation (most common) to Disseminated intravascular coagulation (DIC).[7] MSF is endemic in the Mediterranean area, and recent cases of particular seriousness have been reported with severe clinical presentation.[7]

The aim of our study was to retrospectively analyse the incidence as well as clinical and laboratory parameters of Rickettsioses cases causing MSF in children admitted to the Paediatric Operative Unit of the Policlinico-Vittorio Emanuele University Hospital, University of Catania, Italy, from 1987-2010.

2. Materials and methods

Our study is a retrospective analysis of the incidence of Rickettsioses in childhood and the clinical, immunological and serological parameters of infected patients, observed in children between 2 and 11 years of age admitted to the Paediatric Operative Unit of the Policlinico-Vittorio Emanuele University Hospital, University of Catania, Italy, from 1987-2010, who initially presented with persistent fever of unknown origin.

All included patients had been admitted to our Operative Unit after 7 days of fever, not responding to common antibiotics, and generalised macular-papular erythematous lesions.

We excluded all patients affected by known, previously diagnosed, infectious diseases, chronic disease such as diabetes, renal failure, congenital heart disease as well as genetic and metabolic disorders or undergoing any immune-suppressant therapy.

In order to calculate the incidence of the diseases during the considered years, we divided the patients into 6 subgroups according to chronological parameters:

- Group 1: children admitted from 1987 to 1990;
- Group 2: patients admitted from 1991 to 1994;
- Group 3: subjects admitted from 1995 to 1998;
- Group 4: children admitted from 1999 to 2002;
- Group 5: patients admitted from 2003 to 2006;
- Group 6: patients admitted from 2007 to 2010.

All patients underwent full routine, metabolic and infective blood analyses, including the coagulation profile, inflammatory indexes, immunological profile, and serologic parameters with serum-diagnosis evaluation. The results of these analyses were then consecutively recorded in our electronic database.

Patients also underwent a cardiac, lung and abdominal evaluation by ECG, echocardiography, chest X-ray, abdomen and renal ultrasound scan, in order to exclude any organ dysfunction or failure.

After the results of serological testing, all patients underwent appropriate therapy to eliminate the infection and supportive therapy for associated symptoms.

2.1. Statistical analysis

All routine analyses of numeric values from clinical evaluation are expressed as absolute values in mean and standard deviation (SD).

The percentage statistic values were obtained using the frequency calculation test.

The comparison between percentages was performed by the Chi-Squared Test

3. Results

Our study included 55 patients, 29 males and 26 females, with mean age 5.6 years ±3.12 standard deviation (SD).

The demographic parameters and routine blood analysis of the included patients are shown in Table 1. The immunological and serological blood parameters of the studied patients are shown in Table 2. The clinical features and therapeutic follow-up of the included patients are shown in Table 3.

We found an increasing incidence of MSF in childhood from 1987 to 2010. The incidence of MSF was as follows: 0.16% of hospital admissions (HA) from 1987 to 1990; 0.31% of HA from 1991 to 1994; 0.26% of HA from 1995 to 1998; 0.28% of HA from 1999 to 2002; 0.36% of HA from 2003 to 2006; 0.46% of HA from 2007 to 2010.

In our observation, a confirmed diagnosis of MSF at first hospital admission was achieved in 16 patients (29.09%). All patients (100% of cases) were referred to our Hospital for persistent fever and skin rash, variably associated with other non-specific symptoms including headache, abdominal pain, joint pain, muscular pain, fatigue, and less frequently vomiting, diarrhoea and lack of appetite. In 2 patients (3.63%) we found the presence of bilateral conjunctivitis.

In most cases the history was negative for tick bite; only 16% of cases reported a tick puncture before the onset of symptoms, whereas this was unobserved in 84% of cases.

The presence of the classic Tache noire was observed in 16 cases out of 55 patients affected by MSF (29.09% of cases). This lesion was observed in all cases on the site of the tick puncture if reported and was not painful nor itchy.

Skin rash usually manifested 3-4 days after the onset of fever, with a primarily typical distribution on hands, feet and limbs, and a subsequent spread (after 24-36 hours) to the trunk, neck, face, hands and feet. This evolution and its distribution were not consistent in all patients as they could be altered by the use of various antibiotics.

Lesions initially were maculo-papular with a light pink colour and were irregularly defined. Their centripetal distribution was consistent with a measles rash, an important differential diagnosis.

All patients were admitted to the hospital for a variable period of time, with a minimum of 3 days to a maximum of 14 days (Table 3). Furthermore, fever and symptom duration showed a variable time, lasting from a minimum of 2 days to a maximum of 10 days (Table 3).

All blood parameters and immunological parameters were within normal range, with the exception of inflammatory markers that in most cases were elevated (Table 1).

Table 1
demographic parameters and routine blood analyses levels, expressed as mean and standard deviation, of patients enrolled in our study, stratified by groups of years.

Distribution of patients by range of years	Number of cases diagnosed	Presence of Tache noir	Hb (mg/dl)	RBC cells/mmc	WBC cells/mmc	Leucocyte formula %	Platelet count cells/mmc	VES	Tot. Blood Proteins (g/dl)	Fractionate Blood Proteins (g/dl)	C reactive protein (mg/dl)	Transaminases (UI/l)	Renal function and electrolytes
1987-1990	5 (2 M and 3 F)	1% (1 in 5 cases)	12.38±1.04	4.590.000 ± 0.31	9.340± 4000.42	Neutr. 46.4±25.52 Lymph. 51±25.71 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	198.600±73.93	41.7 ±13.62	6.62±0.16	Alb. 54±4.89 Alpha1 prot: 4.8±0.83 Alpha2 prot: 14.4±2.3 Beta protç 12.2±3.34 Gamma prot: 16.2±3.63	22.31± 13.38	ALT: 56.2±16.16 AST 44.8±20.89	N.R.
1991-1994	10 (5 M and 5 F)	10% (1 in 10 cases)	11.86±1.08	4.590.000 ± 0.49	6.660± 1000.06	Neutr. 41.9±18.65 Lymph. 46.1±18.44 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	208.800±57.05	42.9 ±13.36	6.47±0.33	Alb. 58.3±3.91 Alpha1 prot: 4.2±1.61 Alpha2 prot: 11.8±2.89 Beta prot: 10.8±1.22 Gamma prot: 16±3.82	18.55±11.55	ALT: 39.3±17.02 AST 40.8±10	N.R.
1995-1998	8 (5 M and 3 F)	12.5% (1 in 8 cases)	11.29±1.40	4.570.000 ± 0.44	7.780± 2000.30	Neutr. 50.5±13.92 Lymph. 41.25±14.16 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	256.000±109.94	58.25 ±23.03	6.78±0.76	Alb. 52.87±3.04 Alpha1 prot: 4±1.30 Alpha2 prot: 14.75±2.31 Beta prot: 12.62±1.3 Gamma prot: 15.37±2.44	39.12±29.98	ALT: 39.14±20.57 AST 42.42±11.42	N.R.
1999-2002	7 (5 M and 2 F)	14.28% (1 in 7 cases)	12.40±1.06	4.317.000 ± 0.28	7.928± 4000.14	Neutr. 47.57±18.23 Lymph. 51.71±18.16 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	191.142±30.98	38.55 ±10.98	7.64±2.60	Alb. 62.57±1.81 Alpha1 prot: 3.28±0.48 Alpha2 prot: 8.57±2.14 Beta prot: 9.14±0.89 Gamma prot: 16.85±3.57	10.12±3.89	ALT: 40.7±19.03 AST 41.14±16.48	N.R.
2003-2006	11 (5 M and 6 F)	36.36% (4 in 11 cases)	13.40±3.04	4.550.000 ± 0.27	8.706± 4000.14	Neutr. 40.23±15.14 Lymph. 54.92±18.19 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	248.18±123.40	52.86 ±16.87	6.32±0.66	Alb. 54.09±5.26 Alpha1 prot: 5.06±1.14 Alpha2 prot: 13.74±2.48 Beta prot: 11.76±1.33 Gamma prot: 13.36±4.72	57.53±61.72	ALT: 39.54±19.49 AST 46.36±25.76	N.R.
2007-2010	14 (7 M and 7 F)	57.14% (8 in 14 cases)	12.96±1.54	4.257.000 ± 0.512	7.848± 3546.24	Neutr. 42.22±19.51 Lymph. 55.43±23.72 Monoc. N.R. Eosinoph. N.R. Basoph. N.R.	223.24±82.78	45.23 ±12.14	6.64±0.45	Alb. 55.64±4.28 Alpha1 prot: 6.67±1.12 Alpha2 prot: 13.68±2.35 Beta prot: 10.22±1.24 Gamma prot: 14.44±5.11	25.33±12.45	ALT: 44.2±15.67 AST 42.89±18.12	N.R.

Alb: albumin; ALT: alanine transaminase; AST: aspartate transaminase; F: females; Hb: levels of Hemoglobin; M: males; N.R.: within the normal ranges; RBC: Red blood cells; VES: Erythrocyte sedimentation rate; WBC: White blood cells.

Table 2
immunological and serological blood parameters of patients enrolled in our study, stratified by groups of years.

Distribution of patients by range of years	Serum IgA	Serum IgM	Serum IgG	Complement	Rickettsiae Serum diagnosis OX19	Rickettsiae Serum diagnosis OXK	Rickettsiae Serum diagnosis OX2	Rickettsiae Serum diagnosis OXQ
1987-1990	129.4±19.24	151.02±23.04	1130±58.30	C3 72.78±19.92 C4 48.32±9.80	1/80 (40%)	1/20 (40%) 1/80 (40%)	Negative (100%)	Negative (100%)
1991-1994	71.19±5.54	160.7±15.86	725±85.55	C3 82.2±10.10 C4 32.36±8.96	1/20 (10%) 1/40 (10%)	1/20 (10%) 1/40 (12.5%) 1/80 (20%) 1/320 (10%)	1/20 (20%) 1/40 (30%) 1/320 (10%)	1/20 (12.5%) 1/40 (12.5%)
1995-1998	78.61±7.34	151.62±7.68	1057.25±93.52	C3 66.87±9.18 C4 35.62±4.03	1/40 (12.5%) 1/80 (12.5%)	1/40 (12.5%)	1/160 (12.5%) 1/320 (12.5%)	1/40 (12.5%) 1/640 (12.5%)
1999-2002	82.76±8.24	157.78±9.64	1102.55±63.32	C3 72.77±7.18 C4 42.52±7.24	1/10 (14.25%) 1/20 (28.57%) 1/80 (14.25%)	1/40 (28.57%) 1/80 (14.25%) 1/640 (28.57)	1/20 (14.25%) 1/40 (14.25%) 1/80 (14.25%)	Negative (100%)
2003-2006	167.81±32.12	187.36±22.34	1184.90±86.87	C3 121.37±37.73 C4 60.118±9.10	1/20 (18.18%) 1/80 (18.18%)	1/20 (27.27%) 1/40 (9.09%) 1/80 (9.09%) 1/160 (9.09%)	1/20 (9.09%) 1/160 (9.09%) 1/320 (9.09%)	1/20 (18.18%) 1/80 (18.18%)
2007-2010	79.42±6.22	174.12±13.78	1028.45±82.857	C3 65.57±22.43 C4 46.11±8.30	1/20 (7.14%) 1/80 (21.42%)	1/20 (21.24%) 1/40 (21.24%) 1/80 (21.24%) 1/320 (7.14%)	1/20 (7.14%) 1/40 (21.24%) 1/80 (21.24%) 1/320 (7.14%)	1/20 (21.24%) 1/80 (7.14%)

Studying the serological aspect of *R. conorii* antigens by Weil-Felix and Vidal-Wright serodiagnosis, we noticed a different representation of *R. conorii* antigens over time, corresponding to higher incidence rates of infection in the latter years (Figure 1). Whilst the most representative antigens from 1987 to 1990 were OX19 and OXK, between 1991 and 1994 there was increased expression of the OX2 antigen, and from 1995 to 2010 all four *R. conorii* antigens, including OXQ, were highly expressed. The

Table 3
Clinical features and therapeutic follow-up of patients enrolled in our study, stratified by groups of years.

Distribution of patients by range of years	Presence of Tache noire	Skin rash site	Days of hospital admission	Symptoms duration (days)	Fever duration (days)	Therapy
1987-1990	1% (1 on 5 cases)	Generalized (40%) Hands and inferior limbs (40%) Trunk (20%)	3.6±0.89	5.26±1.34	2.8±1.48	Topical clortetracicline, Ampicillin, Clavulanic acid, Macrolide, Anti-inflammatory therapy
1991-1994	10% (1 on 10 cases)	Generalized (80%) Trunk, hands and feet (20%)	7.1±1.67	5.1±0.87	5±2.30	Topical clortetracicline, Macrolide, Anti-inflammatory therapy
1995-1998	12.5% (1 on 8 cases)	Generalized (75%) Trunk, hands and feet (12.5%) Trunk, face, hands, feet (12.5%)	4.87±1.12	3.5±1.60	5.87±4.54	Topical clortetracicline, Ampicillin, Clavulanic acid, Macrolide, Anti-inflammatory therapy
1999-2002	14.28% (1 on 7 cases)	Generalised (57.14%) Face and superior and inferior limbs (14,.8%) Trunk (14.28%) Hands and feet (14.28%)	9.14±1.89	8.57±3.50	7.92±2.76	Topical clortetracicline, Ceftazidime Macrolide, Anti-inflammatory therapy
2003-2006	36.36% (4 on 11 cases)	Generalised (63.63%) Limbs, Hands and feet (18.18%) Trunk, hands and feet (17.57%)	5.18±1.99	5.5±3.17	5.22±2.92	Topical clortetracicline, Clavulanic acid, Cefpodoxima Proxetil, Macrolide, Anti-inflammatory therapy
2007-2010	57.14% (8 on 14 cases)	Generalised (44.45%) Face and superior and inferior limbs (15.23%) Trunk (14.23%) Hands and feet (46.73%)	3.92±1.20	7.12±2.49	4.15±1.18	Cloramphenicol, Claritromicine Macrolide, Anti-inflammatory therapy

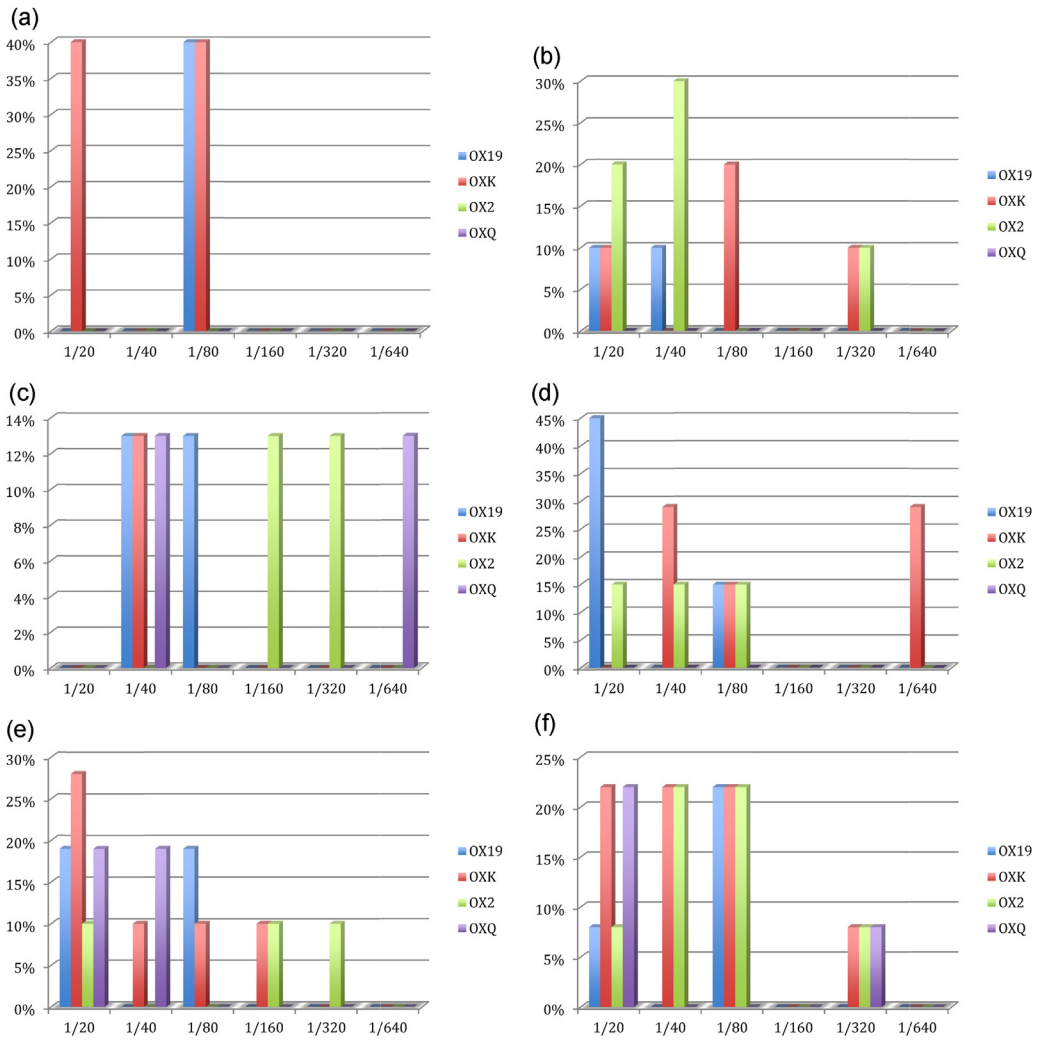

Figure 1. a: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 1987 to 1990
b: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 1991 to 1994
c: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 1995 to 1998
d: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 1999 to 2002
e: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 2003 to 2006
f: Distribution of *R. conorii* antigens, positive to the serum diagnosis of patients included in our study from 2007 to 2010

exception was the years 1999-2002, during which the OXQ antigen was not represented (Figure 1). We also observed a higher incidence of infection in those years in which all four antigens were found positive at serodiagnosis with respect to those years in which only two of the four antigens were represented (1987-1990: 0-16%; 2007-2010: 0.46%; $P<0.005$).

4. Discussion

This study found an increasing incidence of Rickettsia infection causing MSF in children living in Catania, Sicily, Italy, from 1987 to 2010. This was associated with a concurrent change of antigenicity of *R. conorii*, with a higher expression of pathogenic antigens. The widespread incidence of pets living in domestic environments seems to be linked to a higher incidence of *R. conorii* infections.[8]

Rickettsial microorganisms are symbiotic parasites of arthropods, and their life cycle includes a first phase in which these parasites live inside arthropods, such as lice, fleas, mites and ticks, while in a second phase they reproduce inside warm-blooded animals, including dogs, rats, ovine, bovines, and human beings. For some types of Rickettsia, human beings represent a phase of their normal life cycle, whereas for the Rickettsia responsible for exanthematous Typhus, for example, the human being represents the only warm-blooded carrier.[8] Thus close proximity of the different hosts can facilitate transport and subsequent infection.

Rickettsiae are mostly intracellular parasites, with the exception of the Rickettsia responsible for the Quintana fever, which is the unique extracellular microorganism.[9] Their pathogenic action is linked to cellular damage caused by the production of endotoxin acting on the endothelial walls of arteriole and capillaries. This endotoxin can cause inflammatory lesions, with consequent production of nodules, perivascular lesions, sometimes associated with vessel rupture or vessel occlusion, eventually evolving into overt Disseminated Intravascular Coagulation (DIC).[9]

Among the different species of Rickettsiae, *R. conorii* is endemic in the Mediterranean area and is the etiologic agent for the MSF and the Mediterranean exanthematous fever (MEF). Nevertheless, other Rickettsia species also may be present in the Mediterranean area as a consequence of globalization and immigration, although no current studies are available that have explored this.

Rhipicephalus sanguineus, the brown tick of dogs, represents the most common vector of *R. conorii*. The epidemiological course of

MSF is strictly linked to the biological features of this tick, and the infection manifests itself in a seasonal pattern, with a higher incidence between June and October.[9] The common aspect in the history of infected people is daily contact with their household animals, especially dogs.

In our study we found a higher incidence of Rickettsia infection in childhood from 1987 to 2010, also reflecting a greater representation of the four *R. conorii* antigens, as analysed by Weil-felix and Vidal-Wright serum diagnosis. These changes in *R. conorii* antigenicity may be the cause for the higher pathogenicity of this parasite and may be caused by the widespread phenomena of immigration, with changes in the epidemiology of infectious diseases in host countries. In this regard, the presence of new *R. conorii* genotypes by multispacer typing of Rickettsia on skin biopsies has recently been demonstrated. These genotypes have been referred to subspecies groups of *R. conorii*, named *R. conorii* subsp conorii and subsp israelensis.[10]

It is curious that only 16% of cases reported a tick puncture before the onset of symptoms and only in 29.09% of cases was there evidence of the presence of Tache Noire. This observation highlights the non-specific presentation of Rickettsial infections and the absence of typical signs associated with Rickettsia infection, making the differential diagnosis with other infectious diseases more complex. The common clinical signs in our included patients were persistent fever and skin rash, predominantly centripetally distributed, and associated with various non-specific symptoms. In only 2 cases did we observe bilateral conjunctivitis, considering that there have been rare reports of cases with conjunctival infection or secondary ocular involvement of the infection from widespread, itchy skin lesions.[11] An interesting aspect of the studied patients, from a clinical point of view, is the atypical presentation of the diseases. Most patients were admitted in our Paediatric Acute and Emergency Room for fever and skin rash, without any other symptoms or signs of the disease. Therefore, differential diagnosis with other exanthematous diseases was clinically difficult. This is an important aspect to note because this atypical presentation may be the cause for the misdiagnosis of this disease, especially when children are admitted in the Regional Paediatric Ambulatories and are being treated with common antibiotics as a consequence of the misdiagnosis of the real disease. The importance of the knowledge of these atypical presentations requires more detailed data on the real epidemiology of Rickettsioses.

All patients had normal routine blood parameters, including the coagulation profile, and no complications were observed because antibiotic therapy was started soon after the results of serological exams.

It is important to know the epidemiology of Rickettsioses to establish the correct antibiotic therapy (mainly chlaritromicine in paediatric patients) in order to prevent a possible evolution of the disease toward its serious complications. Moreover, the right antibiotic therapy also should be used in those cases in which there is doubt regarding *R. conorii* infection, particularly if the patient's history is positive for any tick puncture or any contact with household animals in the presence of persistent fever.

A bias of our study is the low number of misdiagnoses of infection, which is due to a lack of knowledge of the real epidemiology and incidence of Rickettsioses, as they are incorrectly considered rare infections and more often are treated in the paediatric ambulatory unit without further routine controls, risking the onset of complications and the spread of carriers.

Therefore we want to stress the importance of our study in improving knowledge about this infectious disease, especially in its atypical forms, aiding the paediatrician considering a diagnosis of Rickettsia infection in cases presenting with fever and skin rash but without its typical Tache Noire, and encouraging the scientific population to diagnose those cases of Rickettsia infection to avoid further spread of the disease. Moreover, a more detailed study should involve the Regional Paediatric sites of access within the Paediatric Ambulatories because most of these patients are not then transferred to the referring Hospital but are usually treated by the Paediatric Physicians with wide spectrum antibiotics, resulting in a consequent underestimation of the problem. Therefore, this study may represent the starting point leading to other larger epidemiologic studies.

The aim of this retrospective study was to report a hygienic-epidemiological analysis of MSF infection in childhood, to better identify eventual carriers responsible for the spread of Rickettsia infection, and to highlight the importance of prompt clinical and therapeutic follow-up in order to encourage early diagnosis of the disease, allowing less aggressive but more efficient therapeutic strategies.

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