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1 **Mediterranean spotted fever and peripheral facial nerve palsy: a rare neurological**
2 **complication**

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14 **Keywords:** Mediterranean spotted fever, *Rickettsia conorii*, peripheral facial nerve palsy

15 **Abstract:** Mediterranean spotted fever (MSF) caused by the bacterium *Rickettsia conorii*
16 *conorii* is one of the oldest known tick-borne diseases. It is transmitted by the brown dog tick
17 *Rhipicephalus sanguineus* and occurs mainly in the Mediterranean area. MSF usually presents
18 with a skin rash, high fever, and a characteristic eschar at the tick bite site. The course of this
19 disease may be benign or life threatening. Focal neurological manifestations are unusual. We

20 report the case of a patient who presented with an isolated peripheral facial nerve palsy
21 complicating *R. conorii conorii* infection.

22 **1. Introduction**

23 Mediterranean spotted fever (MSF) is a zoonosis caused by *Rickettsia conorii conorii*, a tick-
24 borne pathogen belonging to the spotted fever group (SFG) rickettsiae. It is transmitted by the
25 brown dog tick *Rhipicephalus sanguineus*. MSF is endemic in North Africa including Algeria
26 and Southern Europe countries bordering the Mediterranean Sea (Rovero and Raoult 2008).
27 MSF may present as benign or life threatening conditions. It is characterized by fever, rash
28 and a black eschar (“tache noire”) at the site of the tick bite, a hallmark of many SFG
29 rickettsioses (Rovero and Raoult 2008). Focal neurological manifestations are unusual. We
30 report the case of a young female patient who presented with peripheral facial nerve palsy
31 complicating *R. conorii* infection.

32 **2. Case Report**

33 A 12 year old girl with no significant medical history presented to the infectious diseases
34 outpatient unit with a six-day history of febrile maculopapular rash associated with arthralgia.
35 Patient history was notable for contacts with dogs. Physical examination revealed fever
36 (39°C), tachycardia (95bpm) and tachypnea (26/min). Cutaneous examination revealed a
37 generalized maculopapular rash, more prominent on the lower limbs. The rash consisted in
38 erythematous indurated lesions, a few millimeters in diameter (Figure 1). Routine laboratory
39 findings showed leukocytosis (13,000 leukocytes/mL and C – reactive protein (CRP)
40 elevation at 76 mg/L. All other parameters were within normal range. Chest radiography did
41 not retrieve abnormalities. Serum samples and a dry swab obtained from the eschar were also

42 sent to the Reference Center for Rickettsial diseases in Marseille, France for specific
43 diagnosis.

44 The patient was started on oral doxycycline 200 mg/day for seven days. On the second day
45 after admission, the patient presented sudden left peripheral facial palsy (Fig. 1). Physical
46 examination revealed asymmetry at rest and onset drooping of left eye. No ocular pain or
47 redness was noted. Otoscope examination showed a normal tympanum on both sides. Head
48 and neck examination did not retrieve any parotid lesion. Neurological examination did not
49 reveal any other abnormality. Contrast-enhanced CT scan of the brain including orbital cuts
50 was normal. Cerebrospinal fluid examination was normal. The patient received oral
51 prednisone at a dosage of 2 mg/kg per day for seven days, and gradually tapered within
52 seven days. The outcome was favorable, with apyrexia after 3 days of treatment. One month
53 later, on a follow up evaluation, the girl had retrieved normal left facial nerve function.

54 Serum samples and the dry swab were secondarily studied in Marseille, France. A *Rickettsia*
55 serological assay was performed. Indirect immunofluorescence (IFI) testing was positive for
56 *R. conorii*, with an Ig G titre of 1:2048 [normal range < 1:128] and IgM titre of 1:256 [normal
57 range < 1:64] (Rovero and Raoult 2008). DNA extraction was obtained from the dry swab
58 sample, and the eluate was screened in real-time quantitative PCR (qPCR) with genus-specific
59 primers and probes targeting a fragment of the *gltA* gene of all spotted fever group *Rickettsia*
60 species (Renvoisé et al. 2012) using a CFX Connect™ Real-Time PCR Detection System
61 (Bio-Rad, Hercules, CA, USA) and the Eurogentec Takyon qPCR kit (Eurogentec, Seraing,
62 Belgium). Since the sample was positive, it was tested with species-specific *R. massiliae* and
63 *R. conorii* qPCR, targeting fragments of an hypothetical protein and the putative
64 acetyltransferase genes, respectively (Renvoisé et al. 2012). DNA extract from cultures of *R.*
65 *massiliae* and *R. conorii* were used as qPCR positive controls. The specific assay for *R.*
66 *conorii* was positive, confirming the diagnosis of MSF.

67 3. Discussion

68 We reported the case of a young female patient who presented with a typical MSF associated
69 with peripheral facial nerve palsy. Although rare, some neurological complications have been
70 described in MSF: meningoencephalitis, myelitis, Guillain-Barré syndrome as well as facial
71 nerve paralyses (Bitsori et al. 2001). Facial nerve paralysis in MSF has been seldom reported
72 in the literature (Bitsori et al. 2001; Mert et al. 2006; Cascio et al. 1998). In a Turkish series of
73 *R. conorii* infection cases, one case only of facial nerve palsy was noted (Mert et al. 2006).
74 Two cases developing facial paralysis as a complication of MSF were reported by Sicilian
75 authors (Cascio et al. 1998). Moreover, Bitsori reported two teenage girls with facial nerve
76 palsy and serological evidence of *R. conorii* infection (Bitsori et al. 2001).

77

78 FBM is a systemic disease, with symptoms caused by vasculitis, which results from
79 proliferation of rickettsiae in vascular endothelial cells. Direct rickettsial invasion of the
80 nervous system has been described in patients with acute neurological complications
81 (Sekeyová et al. 2019). However, cranial nerve palsies occurring in the absence of clinical,
82 laboratory or imaging evidence of meningoencephalitis, are thought to be a consequence of
83 selective vasculitis affecting the respective nerves (Sekeyová et al. 2019). In our report, the
84 diagnosis has been definitely documented using reference methods including direct molecular
85 detection on swab eschar sample and indirect serological IFA assay and, performed in an
86 international referral centre for Rickettsioses (Rovero and Raoult 2008; Renvoisé et al. 2012).
87 The use of molecular tools or cell culture on a skin biopsy specimen from an eschar has been
88 a widespread method to identify *Rickettsia* spp (Parola et al. 2013). However, this technique
89 is invasive and painful for patients, and may be difficult to perform on certain areas of the
90 body (Parola et al. 2013). Swabbing of an eschar is much less painful and invasive than
91 performing a biopsy from the eschar. This sample requires a dry sterile swab that must be

92 rotated vigorously to the base of the eschar, right after the crust has been withdrawn (Parola et
93 al. 2013). In the case of a dry eschar lesion, a wet compress previously soaked with sterile
94 water should be placed on the inoculation eschar for 1 minute before swabbing, to increase
95 the quantity of material swabbed. Moreover, the crust can also be used for rickettsial
96 diagnosis (Parola et al. 2013). Thus, this technique may be performed rapidly, either at the
97 bedside or in outpatient settings. As soon as the samples are sent to a laboratory where qPCR
98 diagnosis is feasible, results can be obtained quickly. This method has shown encouraging
99 results for the detection of different *Rickettsia* species infecting humans in several countries
100 (Bechah et al. 2011; Socolovschi et al. 2012; Khrouf et al. 2016).

101 Therapeutic management in patients presenting neurological complications in MSF relies on
102 antibiotic and corticosteroid therapy (Bitsori et al. 2001; Mert et al. 2006; Cascio et al. 1998).
103 The reference treatment of rickettsial diseases remains doxycycline, including in severe forms
104 of childrens (Parola et al. 2013). Although corticosteroids were administered in our case, as in
105 facial nerve palsy of other or unknown origins, its use remains nowadays discussed (Arıcan et
106 al. 2017).

107 **4. Conclusion**

108 The reemergence of rickettsial infections is occurring in many regions of the world due to
109 human travel and environmental changes, thus clinicians should know the complications
110 related to the disease.

111 This case emphasizes the importance of considering MSF in the differential diagnosis of a
112 patient with fever, rash and facial nerve palsy in endemic areas. A prompt diagnosis is
113 fundamental since early antibiotic treatment significantly improves the outcome of the
114 disease.

115 **Figure Legends**

116 Figure 1, Panel A: Picture of the patient's face showing peripheral facial palsy with loss of the
117 nasolabial fold.

118 Figure 1, Panel B: Picture of the anterior view of the patient's legs, showing generalized
119 erythematous maculopapular rash.

120 Figure 1, Panel C: Picture showing the dark-brown inoculation eschar on the site of the tick's
121 bite.

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