Mediterranean spotted fever with encephalitis

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Rickettsia conorii infection is endemic in the Mediterranean basin, where it is known as Mediterranean spotted fever, also known as Boutonneuse fever and Marseilles fever. We report the case of a 66-year-old diabetic man who presented a severe form of the disease, complicated by acute renal failure, thrombocytopenia and encephalitis. Diagnosis was confirmed by indirect immunofluorescence assay. Despite appropriate treatment, severe neurological sequelae have remained. Medical literature on encephalitis caused by R. conorii is also reviewed.

Introduction

In southern Europe, rickettsial spotted fever, which is caused by Rickettsia conorii, is known as Mediterranean spotted fever (MSF), Boutonneuse fever and Marseilles fever (Walker & Raoult, 2000). During the 1970s and 1980s, an increased incidence of spotted fever rickettsioses was noticed in many parts of the world, particularly in Spain, France and Italy (Raoult et al., 1986; Walker & Raoult, 2000). R. conorii is transmitted to humans by tick bite. Accordingly, cases occur mainly in the summer months in the Mediterranean basin (Font Creus et al., 1991; Raoult et al., 1986).

MSF is usually a benign self-limited exanthematous febrile illness (Font Creus et al., 1991; Raoult et al., 1986). However, in studies of large series of patients from France and Spain severe and fatal cases of the disease have been described (Font Creus et al., 1991; Raoult et al., 1986). In these studies and in other case reports, disease complications have included acute renal failure, thrombocytopenia, myocarditis, pneumonitis, gastric haemorrhage, shock and multiple organ failure (Amaro et al., 2003; Font Creus et al., 1991; Raoult et al., 1986; Walker et al., 1987). Furthermore, a few reports in the literature have pointed out that central nervous system involvement may occur in the course of MSF, including problems such as meningitis (Ezeleta et al., 1999; Tzavella et al., 2006), encephalitis (Amaro et al., 2003; Benhammou et al., 1991; Ezeleta et al., 1999; Marcos Dolado et al., 1994; Texier et al., 1984; Walker et al., 1987) and myelitis (Ezeleta et al., 1999). Recently, we have seen a patient with MSF complicated by encephalitis.

Rickettsioses are emerging infectious diseases, and a review of this topic seems timely.

Case report

A 66-year-old diabetic man was admitted to Hospital Universitario Virgen de las Nieves in June because of fever, rash and altered mental status. The patient had previously been in contact with dogs in a rural area, since he regularly spent his weekends in a village. He had remained well until 7 days before admission, when he began to suffer from malaise, fever, headache and myalgia. In the morning of his hospitalization, the patient presented slurred speech.

At presentation his temperature was 37 °C, his blood pressure was 157/79 mmHg and his pulse was 120 beats min−1. Physical examination disclosed a popular rash over his trunk, palms and soles, and a black scar 1 cm in diameter on his right forearm. He was severely obtunded. The remainder of the physical examination showed normal results.

His haemoglobin level was 14 g dl−1, his white blood cell count was 7100 cells μl−1 (86 % neutrophils, 9 % lymphocytes and 5 % monocytes) and his platelet count was 81 000 platelets μl−1. His C-reactive protein level was 45 mg dl−1. His prothrombin and partial thromboplastin times (blood coagulation times) were normal. He also had the following: 271 mg glucose dl−1, 5.13 mg creatinine dl−1, 269 mg urea nitrogen dl−1, 92 U aspartate aminotransferase l−1 (normal range 10–40 U l−1), 81 U alanine aminotransferase l−1 (normal range 10–40 U l−1), 2.1 mg total bilirubin dl−1 and 102 U γ-glutamyltransferase l−1 (normal range 7–32 U l−1). Urinalysis and a chest radiograph were unremarkable.
A computed tomography (CT) scan of the head, without the administration of contrast material, revealed no abnormalities. A lumbar puncture was done. Cerebrospinal fluid (CSF) sampling exhibited 2400 red blood cells µl\(^{-1}\), 2 leukocytes µl\(^{-1}\), 55 mg protein dl\(^{-1}\) and 95 mg glucose dl\(^{-1}\). Routine microbiological cultures and PCR for herpes simplex virus from the CSF were negative, as were two blood culture sets. Magnetic resonance imaging (MRI) showed increased subcortical white matter signal abnormalities on diffusion, flair and T2-weighted sequences in the frontal, parietal and occipital lobes (Fig. 1). The splenium of the corpus callosum, the limbic parahippocampal region, the cerebellar peduncles and pons were also affected. The lesions were bilateral, but predominating in the left cerebral hemisphere, shown using mass effect and enhancing of the MRI image with gadolinium. The patient was transferred to the Intensive Care Unit, Hospital Universitario Virgen de las Nieves, and needed assisted mechanical ventilation. Doxycycline treatment was started (100 mg every 12 h intravenously) and maintained for 10 days. After 7 days of treatment, the fever and rash subsided. The acute renal failure also resolved. However, he continued to require mechanical ventilation. On the 20th hospital day, an indirect immunofluorescence assay for \textit{R. conorii} was performed, showing an antibody titre of 1/160; therefore, no more dilutions of the serum were performed. Serology had been negative at the time of admission. The patient was discharged from the Intensive Care Unit on the 34th hospital day, with a flaccid quadriplegia and aphasia. Aphasia and right spastic hemiplegia persisted even after 1 year of follow-up. A new MRI scan for control purposes 1 year later showed subcortical lesions of encephalomalacia in the regions previously affected.

**Discussion**

The diagnosis of MSF in this patient was straightforward. The disease occurred in summer, with the characteristic symptoms of fever, rash and eschar. A serological test was confirmatory. The clinical course was complicated by acute renal failure, thrombocytopenia and altered mental status. MRI showed disseminated and extensive brain lesions.

We searched world medical literature back to 1948 using the Medline database. We used the following key words: meningitis, meningoencephalitis, encephalitis and central nervous system infection, which were cross-matched with \textit{R. conorii}, MSF, Boutonneuse fever and Marseilles fever. We also reviewed the references in the papers found related to the topic. It is evident that the separation of the clinical syndromes of aseptic meningitis and encephalitis is not always easy. Therefore, we considered encephalitis caused by \textit{R. conorii} to be present when a patient met the following criteria: (i) a diagnosis of MSF according to standard criteria (Font Creus et al., 1991; Raoult et al., 1986; Walker & Raoult, 2000), (ii) acute symptoms of brain dysfunction, and (iii) inflammatory brain lesions evidenced by necropsy or suggested by neuroimaging techniques.

In this search, we found 29 cases of MSF diagnosed concomitantly with encephalitis or meningoencephalitis. Ten of these cases were ruled out because of a lack of details in relation with the diagnosis of encephalitis. Eight patients were ruled out because neuroimaging was normal (or not performed) and no necropsy studies were carried out either. Five cases were discarded because the diagnosis of MSF was doubtful, either on clinical grounds and/or on the basis of microbiological studies. Finally, six case reports from literature met convincingly our criteria for encephalitis, illustrating the major involvement of the central nervous system in \textit{R. conorii} infection. In contrast, Rocky Mountain spotted fever, an infection caused by \textit{Rickettsia rickettsii}, frequently presents neurological disease (Walker & Raoult, 2000).

The clinical features of the six patients from the literature and the one patient described herein are summarized in

![Fig. 1. MRI diffusion weighted imaging (a), T2-weighted (b) and flair sequences (c) showing extensive signal hyperintensity, predominating in subcortical white matter of the left hemisphere.](https://www.microbiologyresearch.org)
Table 1. Data from the seven reported cases of MSF with encephalitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient’s age (years)/sex</th>
<th>Epidemiological data</th>
<th>Previous illnesses</th>
<th>Clinical manifestation</th>
<th>Brain CT scan findings</th>
<th>Brain MRI findings</th>
<th>CSF findings</th>
<th>Diagnosis</th>
<th>Treatment (days)</th>
<th>Outcome and comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaro et al. (2003)</td>
<td>47/M</td>
<td>Portugal</td>
<td>NR Summer</td>
<td>None</td>
<td>Headache, seizure, stiff neck</td>
<td>Normal</td>
<td>ND</td>
<td>ND</td>
<td>Immunohistochemistry on skin</td>
<td>Death in 14 h after hospitalization; necropsy was performed</td>
</tr>
<tr>
<td>Benhammou et al. (1991)</td>
<td>6/M</td>
<td>Morocco</td>
<td>NR July</td>
<td>None</td>
<td>Fever, eschar, arthritis, intercurrent illness, staphylococcal infection</td>
<td>Headache, seizure, stiff neck</td>
<td>Hypodensity in both internal capsules</td>
<td>ND</td>
<td>Pleocytosis</td>
<td>IFA Thiamphenicol (15), corticosteroids (21)</td>
</tr>
<tr>
<td>Ezpeleta et al. (1999)</td>
<td>53/F</td>
<td>Spain</td>
<td>– July</td>
<td>Adult coeliac disease</td>
<td>Fever, eschar, arthritis, intercurrent illness, staphylococcal infection</td>
<td>Confusion, meningismus, facial paralysis, bilateral Babinski, hypotension, pleural effusion</td>
<td>Diffuse lesions in subcortical white matter of left frontal lobe, cerebral peduncles and corpus callosum</td>
<td>Lymphocytic pleocytosis</td>
<td>IFA Cefotaxime*, isoniazid*, ethambutol*, rifampicin*, streptomycin*, acyclovir*, metilprednisolone*, doxycycline*</td>
<td>Alive; spastic paraplegia as sequelae</td>
</tr>
<tr>
<td>Marcos Delado et al. (1994)</td>
<td>65/M</td>
<td>Spain</td>
<td>NR Summer</td>
<td>Diabetes</td>
<td>Fever, eschar, myalgia</td>
<td>Confusion, urinary incontinence, ataxia, bilateral Babinski</td>
<td>Diffuse hypodensity in subcortical white matter</td>
<td>Lymphocytic pleocytosis</td>
<td>IFA Doxycycline (7)</td>
<td>Alive without sequel</td>
</tr>
<tr>
<td>Texier et al. (1984)</td>
<td>20-day-old newborn/F</td>
<td>France</td>
<td>+ August</td>
<td>None</td>
<td>Fever, eschar, eschar, intercurrent illness, staphylococcal infection</td>
<td>Inactivity, seizure</td>
<td>ND</td>
<td>ND</td>
<td>Erythrocytes, lymphocytic pleocytosis, elevated protein, hygylorrhachia</td>
<td>IFA Ampicillin*, gentamicin*, spiramycin*</td>
</tr>
<tr>
<td>Walker et al. (1987)</td>
<td>77/F</td>
<td>Spain</td>
<td>NR Summer</td>
<td>Diabetes, hypertension</td>
<td>Fever, eschar, myalgia, cough, hypotension, renal failure, eschar</td>
<td>Headache, stupor</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>IFA Amoxicillin (11), tetracycline (1)</td>
</tr>
<tr>
<td>PR</td>
<td>66/M</td>
<td>Spain</td>
<td>+ June</td>
<td>Diabetes</td>
<td>Fever, malaise, eschar, acute renal failure, thrombocytopenia</td>
<td>Headache, obtundation, facial quadriplegia, aphasia</td>
<td>Diffuse subcortical lesions in white matter in frontal, parietal and occipital lobes, corpus callosum, cerebral peduncles, post and limbic area also affected</td>
<td>Erythrocytes</td>
<td>IFA Doxycycline (10)</td>
<td>Alive; aphasia and right spastic hemiplegia as sequelae</td>
</tr>
</tbody>
</table>

IFA, Indirect fluorescent antibody test; ND, not done; NR, not reported; PR, present report.
*Treatment duration not reported.
Table 1. The patients comprised a newborn, a child and five adults. All patients presented with severe disease with several complications, along with fever and rash. One patient had no eschar. Interestingly, thrombocytopenia occurred in five patients, and three cases exhibited acute renal failure. The neurological manifestations were dominated by the altered state of consciousness. There were no cranial nerve palsies. Stiff neck was registered in only one patient. Three patients presented seizures. A brain CT scan was performed for five patients, showing abnormalities for two of them. MRI of the brain was performed for two patients; in both patients the MRI showed diffuse alterations in the cerebral lobes, cerebellar peduncles and corpus callosum. CSF was analysed in five patients and showed minor abnormalities. Two patients showed erythrocytes in their CSF, a finding that also may be due to a traumatic lumbar puncture. Three patients died. Among the four patients who survived only one was without sequelae. Sequelae were severe in the remaining three, despite appropriate treatment.

Rickettsia invades and multiplies in vascular endothelial cells, resulting in widespread vasculitis of capillaries, arterioles and small arteries (Walker & Raoult, 2000). Walker and colleagues have studied the brain lesions caused by R. conorii in three patients at necropsy. In two cases of South African tick bite fever, the histopathological features were foci of vasculitis in the brain, consisting of mononuclear leukocyte infiltrating the blood vessel wall and perivascular space (Walker & Gear, 1985). There was also mild mononuclear leukocytic leptomenigitis. The distribution of lesions correlated with numerous rickettsiae observed by means of direct immunofluorescence in the histopathological sections. In one case of MSF, the brain showed prominent perivascular lymphohistiocytic infiltrates, but rickettsiae were not found in the inflammatory lesions (Walker et al., 1987). Necropsy showed petechial haemorrhage within the brain in another patient (Amaro et al., 2003), and granulomatous inflammation and coagulative necrosis of the brain in a newborn (Texier et al., 1984).

The clinical picture, in an appropriate epidemiological setting, is still the mainstay of diagnosis. A definitive diagnosis can only be made by culture of a rickettsial organism in a shell vial or molecular biology analysis of clinical samples (Amaro et al., 2003). In the absence of these techniques, immunohistochemistry of skin lesions may reveal rickettsiae (Raoult et al., 1986). Serology is the usual method to confirm the diagnosis in clinical laboratories. Among the various techniques available, immunofluorescence assay is accepted widely as the reference method (Brouqui et al., 2004). However, determination of antibodies to rickettsiae has two main disadvantages. First, a seroprevalence of antibodies to rickettsiae, from 11 to 26%, is recognized among numerous populations in endemic zones (Raoult et al., 1986). Second, IgM and IgG are not usually detected until 7–15 days after disease onset (Brouqui et al., 2004; Tzavella et al., 2006) and therefore provide a retrospective diagnosis.

The standard regimen for MSF consists of 200 mg doxycycline (orally or intravenously), daily for 3–14 days, depending on the clinical course (Jensenius et al., 2004). Most patients will improve within the first 24 h after the start of therapy; therefore, shorter regimens have been proposed. Doxycycline (5 mg kg\(^{-1}\) every 12 h in children, and 200 mg kg\(^{-1}\) every 12 h in adults) for 1 day is the treatment of choice for some experts (Font Creus et al., 1991). This dosage has minimal risk of tooth staining and bone toxicity in children. Walker & Raoult (2000) have even proposed a single-dose treatment with 200 mg doxycycline in adults. However, in adults with a more severe form of the disease, treatment should be prescribed until the patient is afebrile for 24 h.

Doxycycline is recommended for treatment of encephalitis caused by R. rickettsii (Tunkel et al., 2008). However, adequate CSF and/or central nervous system penetration of doxycycline may be an issue of concern. It is appreciated that ill patients treated with doxycycline should be given a loading regimen of 200 mg intravenously every 12 h for the first 72 h to achieve steady-state serum concentration and early therapeutic effect (Cunha, 2000). In fact, among the three patients who received doxycycline in Table 1, permanent and severe neurological sequelae were observed in two.

Oral josamycin, a macrolide antibiotic, has proved efficient at a dose of 1 g every 8 h for 5 days [50 mg (kg body weight\(^{-1}\) every 12 h in children] (Bella et al., 1990). So, it may be an alternative in children and pregnant women (Walker & Raoult, 2000). Chloramphenicol, the newer macrolides and fluoroquinolones may be alternatives to doxycycline too (Jensenius et al., 2004).

**References**


