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Case Report

Meningitis with cranial polyneuritis and cavernous sinus thrombosis by *Borrelia crocidurae* First autochthonous case in Europe

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ABSTRACT

Borrelia crocidurae is endemic in West Africa, where it represents the leading cause of tick-borne relapsing fever (TBRF). TBRF typically presents with high fever and systemic symptoms, followed by recurrent episodes. Neurological complications may occur during febrile relapses. *B. crocidurae* is considered the most neurotropic agent of TBRF and is associated to severe neurological manifestations *i.e.* meningitis and encephalitis.

To date, European cases of *B. crocidurae* infection have been reported in travelers returning from endemic areas. We report the first autochthonous case in Europe of *B. crocidurae* infection, presenting as meningitis with cranial polyneuritis and cavernous sinus thrombosis that were not preceded by classic febrile recurrences.

Introduction

Borrelia crocidurae is the major etiologic agent of tick-borne relapsing fever (TBRF) in West Africa, where it is endemic and considered the most prevalent infective agent in Senegal (Reboudet and Parola, 2006; Cutler, 2010).

In Europe, only imported cases have been reported, mostly in travelers returning from Senegal (Million et al., 2009; Tordini et al., 2006; Bottieau et al., 2012; Eldin and Parola, 2018). TBRF is characterized by high fever with recurrent episodes, systemic symptoms, such as headache and myalgias, sometimes rash, lymphadenopathy, hepato-splenomegaly and bleeding. First febrile episode typically lasts 3–6 days, and afterwards symptoms recur with less severe relapses (Chikeka and Dumler, 2015). Neurological complications may occur during subsequent relapses, presenting as lymphocytic meningitis, encephalitis, cranial neuritis (mostly of facial nerve) and, less frequently, myelitis, radiculitis and neuropsychiatric disturbances (Castilla Guerra et al., 2016; Cadavid and Barbour, 1998).

Here, we report the first autochthonous case of *B. crocidurae* infection in Europe.

At presentation, the case was not characterized by a classic recurrent fever, but as meningitis with cranial polyneuritis and cavernous sinus thrombosis after a prior episode of low-grade fever.

Case report

On July 2016 a 51 year-old woman was moved to our Infectious Disease Clinic from the Hospital of Umbria Region with the suspicion of viral meningo-encephalitis. The patient was a farm labourer employed in viticulture, coming from Macedonia and living in Italy from 15 years. She was admitted for a ten-day history of headache and vertical diplopia associated with transient low-grade fever, up to maximum 37,5 °C two days before hospitalization. She was affected by hypertension, hypothyroidism and gastro-esophageal reflux. She denied any tick bite and recent

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travels outside Italy except for a visit to her relatives in the country of origin in 2011. Cerebrospinal fluid (CSF) analysis showed mononuclear pleocytosis (100 cells/μl) with normal glucose and protein concentrations. Bacterial cultures were negative and empirical therapy with acyclovir was started. In the following days, the patient developed neurological worsening with bilateral peripheral facial paresis and was transferred to our ward for further neurological analyses.

At our first evaluation, the patient was afebrile, presented bilateral VII cranial nerves involvement, neck stiffness, right side vertical gaze paresis (IV cranial nerve involvement), bilateral lateral gaze palsies (III and VI cranial nerves), left facial hypoesthesia (V cranial nerve) and bilateral chemosis. The CSF showed increasing mononuclear pleocytosis (200 cells/μl), hyperprotidorrachia and normal glycorrhachia. Chemiluminescent ELISA test (DiaSonBorrelia IgM and IgG) and molecular screening for Herpes viruses and *Mycobacterium tuberculosis* on serum and CSF results were negative.

In the next few days, the patient's clinical condition deteriorated with appearance of bilateral tinnitus and painful left-side facial paresthesias. The brain magnetic resonance imaging (MRI) showed bilaterally mild increased density of the cavernous sinuses, enlarged superior ophthalmic veins, enhancement of the mesial temporal meningeal lining, involvement of the labyrintic segments of the facial nerves, geniculate ganglia and pituitary gland, with no signs of central face and/or paranasal sinuses infections (Figure 1, Panel A, B, C, D). The diagnosis of meningitis with cranial polyneuritis and cavernous sinus thrombosis was made. Anticoagulant and steroid therapy were administered, and acyclovir was replaced with ceftriaxone 2 g qd and doxycycline 100 mg bid. CSF and serum samples were sent to the Italian National Institute of Health for *Borrelia* spp. investigation.

Methods

DNA was extracted from the CSF specimen using QIAamp DNA mini kit (QIAGEN, Hilden,Germany) according to the manufacturer's instructions. DNA sample was positive for real-time PCR 16S rRNA gene of *Borrelia* spp. (Rauter et al., 2002). Consequently, the sample was screened for *B.burgdorferi* sensu lato complex and Borrelia relapsing fever group by using real-time PCR targeting the *ospA* and *glpQ* genes, respectively (Halperin et al., 2006; Potkonjak et al., 2016). The *ospA* PCR assay was negative while a positive result was observed with the *glpQ* target, confirming the presence of the Borrelia relapsing fever. A primer set for the flagellin B gene was used for Borrelia identification (Potkonjak A et al., 2016) and the nucleotide sequence of the amplicon obtained (340 bp) showed a 100% similarity with *B. duttonii* (GenBank accession number no GU357618) and *B. crocidurae* (GenBank accession number no. X75204). Two species-specific real time PCRs were employed to discriminate *B. duttonii/B. recurrentis* from *B. crocidurae*, targeting *recN* and *glpQ* genes, respectively (Elbir et al., 2013). Only the specific *glpQ* assay was positive, showing that the etiologic agent of infection was *B. crocidurae*.

In the next three weeks, a progressive improvement of clinical signs and normalization of CSF were observed so that ceftriaxone and doxycycline were discontinued after 4 and 6 weeks respectively, together with a withdrawal of steroid therapy. A progressive improvement of brain MRI findings was registered (Figure 1, Panel E, F, G, H) so that, after three months, anticoagulation was also stopped.

At 6 months, an almost full remission of the neurologic signs was observed, with persistence of a slight deficit of the bilateral facial paresis.

Discussion

We report a case of *Borrelia crocidurae* infection that presents some relevant aspects.

Our patient represents the first autochthonous case of *B. crocidurae* infection observed in Europe. In this regard we need to emphasize some limitations for this particular clinical case, essentially due to the lack of information about the distribution and role of soft ticks in most parts of Europe. *B crocidurae* can be transmitted to humans from small mammals by *Ornithodoros sonrai* ticks in West Africa and in most arid parts of North Africa (*i.e.* Senegal, Gambia, Togo, Mauritania, Mali and Morocco). However, other soft ticks can act as vector for *B. crocidurae*. *B. crocidurae* DNA also was detected in *Ornithodoros erraticus* and in *Ornithodoros marocanus* complex, ticks present in Italy and found in the arid areas of Morocco and the Iberian Peninsula (Starkoff, 1956; Souidi et al., 2014; Boinas et al., 2011). In this view, we can speculate that more *Ornithodoros* species may operate as a vector of TBRF (Diatta et al., 2010). Furthermore, these ticks are characterized by

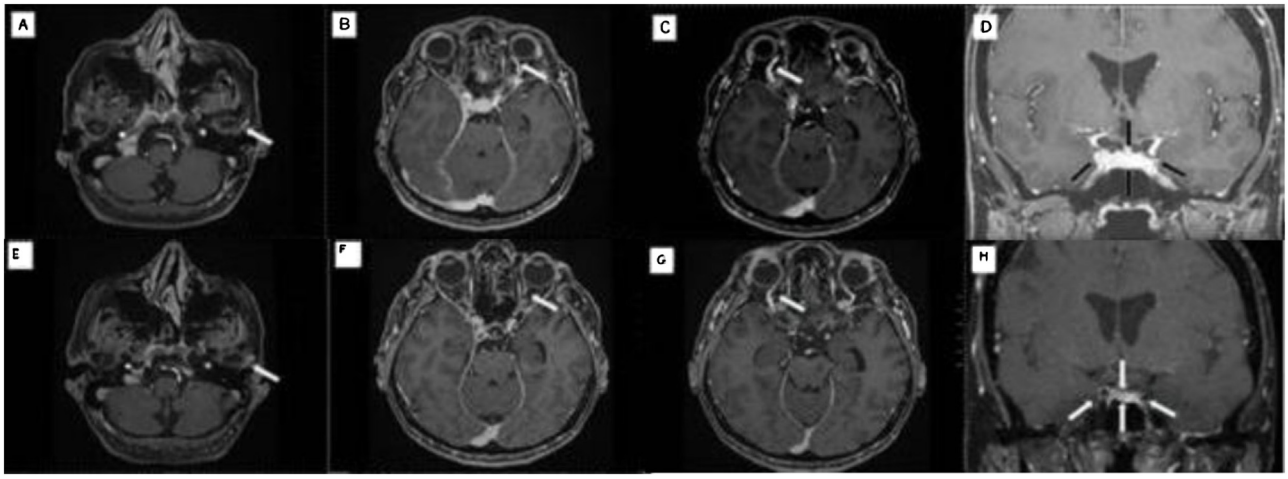

Figure 1. Baseline brain MRI with contrast (A, B, C,D) and follow up brain MRI after 3 months (E, F, G, H).
A: Contrast enhancement in the course of the left seventh cranial nerve (white arrow); **B:** ectasia of the ophthalmic vein in the left eye (white arrow); **C:** ectasia of the ophthalmic vein in the right eye (white arrow); **D:** contrast enhancement in the cavernous sinus bilaterally (black arrows); **E:** reduction of contrast enhancement in the course of the left seventh cranial nerve (white arrow); **F:** reduction of ectasia of the ophthalmic vein in the left eye (white arrow); **G:** reduction of ectasia of the ophthalmic vein in the right eye (white arrow); **H:** reduction of contrast enhancement in the cavernous sinus bilaterally (white arrows).

remarkable longevity, surviving for 7 years in absence of feeding, and the carried spirochetes remained viable over a 5-year period of starvation (Donaldson et al., 2016). This significant longevity has suggested these vectors as possible reservoirs for infection, and various species of squirrels and mice are believed to be significant natural hosts for *Ornithodoros* ticks in many regions. Moreover, global travel, including international adventure tourism in rural and remote places, climatic changes and multiethnic migration may promote the dissemination of vectors, contributing to the spread of vector-borne diseases.

A further relevant aspect of *O.erraticus* is its close association with traditionally managed pig farms in the central and southern parts of Iberian Peninsula, where this and other species of *Ornithodoros* represent the vectors of African swine fever virus (ASFV) occurring in Europe and an effective reservoir for both ASFV and *Borrelia* species. In these regions *O.erraticus* microhabitats are most common in buildings using traditional dry stone or adobe-walled animal housing (Boinas et al., 2011). Our patient did not move outside Italy before the onset of illness but, interestingly, she was a farm labourer, although a clear exposure to animals and their environment was not recognized.

From a clinical viewpoint, our patient presented neurological manifestations that were not preceded by classic febrile recurrences and *B. crocidurae* infection was diagnostically confirmed by molecular methods. Severe neurological complications of TBRF may develop in the course of *B. crocidurae* infection, usually during the first recurrence (Cadavid and Barbour, 1998). Clinical studies demonstrated that severe neurologic complications occur more often than expected with a high neurotropism (Cadavid and Londono, 2009; Goutier et al., 2013; Eldin and Parola, 2018).

In our patient, several neurological signs are shared by both meningo-polyneuritis and cavernous sinus thrombosis, *i.e.* the third through fifth cranial nerves involvement. Conversely, bilateral conjunctival chemosis and involvement of peripheral seventh/eight cranial nerves are more specific for cavernous sinus thrombosis and cranial polyneuritis, respectively. Brain RMN also confirmed the clinical hypothesis of coexistence of both conditions.

Finally, cavernous sinus thrombosis is usually a late complication of infections of the central face or paranasal sinus. In this case, neither sinusitis nor other bacterial agents except *B. crocidurae* were detected and it is worth noting that *B. crocidurae* infection in a murine model was followed by vascular microemboli and symptomatic involvement of the central nervous system, possibly as result of *B. crocidurae* erythrocyte aggregation and rosetting (Shamaei-Tousi et al., 1999; Nordstrand et al., 2000). This histopathologic phenomenon may further contribute to the peculiar neurotropism and highest frequency of severe neurological complication observed in *Borrelia crocidurae* infection, compared with other TBRF species associated with central nervous system involvement, i.e. *B. duttonii*, *B. turicatae* and *B. hispanica* (Cadavid and Londono, 2009; Eldin and Parola, 2018; Goutier et al., 2013)

In conclusion, our patient represents the first autochthonous case of *B. crocidurae* infection reported in Europe, however no clear *Ornithodoros* exposure was documented. This finding focuses the attention on the role of new ecosystems and routes for spread of African TBRF and other vector borne diseases.

Due to its peculiar neurotropism, *B. crocidurae* should be included among the emerging agents of severe neurological syndromes, besides classic TBRF disease.

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Conflict of interest

None.

Ethical approval

The authors declare that the ethical approval was not required for this study.

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