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CASE REPORT

Neurobrucellosis: diagnostic and clinical management of an atypical case

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SUMMARY

Brucellosis is the most common zoonosis in the world and it is caused by ingestion of foods contaminated by *Brucella* spp. that is able to avoid the immune system and can involve every organ system. The bacteria may affect the Central Nervous System (CNS) directly or using phagocytic cells with the way of the "Trojan Horse Model".

Meningitis is the most common form of neuro-brucellosis (NB) but other neurological manifestation, with variable onset, such as severe encephalic involvement, neuropathy, vascular damage, radiculitis and hydrocephalus might happened. NB may manifest itself with an acute or chronic onset and could be the only manifestation of the infection or appearance during the systemic disease. Frequently the diagnosis might be very difficult and the clinical characteristics and the microbiological demonstration in the blood and in the CSF are necessary. The prognosis of brucella meningitis is generally better than other forms of chronic meningitis except for encephalitis or spinal cord involvement. The treatment is based on the combination of two or three antibiotics to achieve normalization of the cerebrospinal fluid parameters otherwise relapse are relatively frequent.

We describe an atypical case of brucellar meningitis with many stroke-like signs, think as recurrent cerebrovascular events and treated with antithrombotic therapy, but without meningeal syndrome.

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INTRODUCTION

Brucellosis is the most common zoonosis and is endemic in many parts of the world, especially in countries that do not have good effective and standardized public health and animal health programs.

The Mediterranean Basin, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East are areas currently listed as high risk (http://www.cdc.gov; http://www.ecdc.europa.eu; Brucellosis surveillance 1991; Pappas *et al.,* 2005; Pappas *et al.,* 2006; Young E. 2010).

Brucella is Gram-negative, small non-motile, non-encapsulated, non-spore-forming cocco-bacillus, without flagella or pili, that grow slowly in medium containing 5%-10% CO_2.

Brucella is able to invade phagocytic and non-professional phagocytic cells and to survive and replicate in specialized endosomes called "brucellosomes", to avoid the immune system; the specie *B. melitensis* presents the major tropism for neural tissue.

Brucellosis may present with a broad clinical spectrum of clinical manifestations, and is typically transmitted to humans by ingestion of unpasteurized milk, cheese or through occupational exposure to infected animals like sheep, camels, cattle, goats and swine. Direct contact with infected animals or their secretions through skin lacerations, conjunctival inoculation and inhalation of infected aerosol may constitute the effective transmission route of the occupational exposure (farmer, veterinarians, laboratoritians) (Corbel M.J. 1997; Farrell *et al.,* 1976, Hatami *et al.,* 2010; Hatami *et al.,* 2003; Russo *et al.,* 2009; Young E. 2010).

NB is the most serious but less common complication of brucellosis. NB may involve CNS and peripheral nervous system (PNS) with an incidence of global neurologic complications around 2%-5% (Boudur *et al.,* 2006; Brucellosis surveillance 1991; Ceran *et al.,* 2011, Hatami *et al.,* 2010; Karsen *et al.,* 2012; Nichols E. 1951; Tzur *et al.,* 2017; Dreshai *et al.,* 2016).

Brucella may affect the Central Nervous System (CNS) directly with the infection of the endothelial cells of the cerebral blood barrier or using phagocytic cells with the way of the "Trojan Horse Model". Infection of CNS via neural route, as *Listeria, Rhabdovirus* and *Cercopitecine Herpesvirus* B, is not demonstrated (Drevets D.A. 2004; Pappas G. 2005).

The most frequent presentation is meningitis that may present an acute or chronic onset and may occur either as the only site of infection or in the context of systemic disease and represent 17% - 74% of the cases of NB (Bounza *et al.,* 1987; Ceran *et al.,* 2011; Guven *et al.,* 2013 *et al.,* 2013; Hatami *et al.,* 2010; Karsen *et al.,* 2012; Turel *et al.,* 2010).

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Onset varies from abrupt to indolent. In children was usually reported to have an acute presentation (Bouza *et al.,* 1987; Ceran *et al.,* 2011; Erdem *et al.,* 2013; Guven *et al.,* 2013; Hatami *et al.,* 2010; McLean *et al.,* 1992; Ranjbar *et al.,* 2009; Shakir *et al.,* 1987; Young *et al.*, 2010; Tzur *et al.* 2017; Pagliano *et al.,* 2015; Pagniali *et al.,* 2016). The infection, as tuberculosis and sarcoidosis, has a predilection for the base of the cranium, thereby involving the cranial nerves.

Granulomatous inflammation within the subarachnoid space may block cerebrospinal fluid (CSF) re-uptake by arachnoid villi, causing hydrocephalus (Hanefi *et al.,* 2009; Shakir *et al.,* 1987).

Transient ischemic attacks and venous thrombosis are meningo-vascular uncommon complications of NB (3%) (Guven *et al.,* 2013; Dreshaj *et al.,* 2016).

There is no consensus about the precise diagnosis of NB.

Diagnostic criteria for NB proposed in literature are (Erdem *et al.,* 2013, Guven *et al.,* 2013.):

1) The presence of consistent clinical symptoms either with meningitis or meningoencephalitis.
2) Consistency of typical CSF findings with meningitis (protein concentrations >50 mg/dL, leukocytes over 10/mm^3 and glucose to serum glucose ratios <0,5).
3) Positive bacterial culture or serological test results for brucellosis in blood specimens (positive Rose Bengal test and serum tube agglutination with a titre ≥1/160) or in CSF (positive Rose Bengal test or serum tube agglutination with any titre) or positive bone morrow culture.
4) Findings of cranial CT or RMN compatible.

There are four IgG subclasses anti-*Brucella*, with the type-4 subclass typical of predominating in three-quarters of patients with chronic brucellosis (Araj G.F. 2010; Erdem *et al.,* 2013).

According to the results of Istanbul-2 study the sensitivities of the principal tests were as follows: serum standard tube agglutination (STA): 94%; cerebrospinal fluid STA: 78%; serum Rose Bengal test (RBT): 96%; CSF RBT: 71%; automated blood culture: 37%; automated CSF culture: 25%: conventional CSF culture: 9% (Erdem *et al.,* 2013).

Biomolecular diagnostic methods (real-time PCR) seem to be promising in the diagnosis and follow-up of NB (Araj G.F. 2010).

According Istanbul-3 Study 45% of NB cases has pathological neuroimaging finding including: meningeal inflammation with post-contrastographic enhancement, cranial nerve involvement, brain abscess, spinal nerve roots enhancement, arachnoiditis, granulomas, white matter changes, and vascular changes (Ceran *et al.,* 2011; Erdem *et al.,* 2016).

NB's differential diagnosis is with cerebral infections of basal-skull, as tuberculosis and sarcoidosis, and with neuropathy during a case of brucellosis and in cases of psychiatric manifestations encountered in endemic areas for brucellosis (Hatami *et al.,* 2010; Hatami *et al.,* 2003; Karsen *et al.,* 2012; Tunkel A. 2010).

Patients who suffer for diffuse CNS involvement (severe encephalitis or spinal cord disease) had a worse prognosis with low mortality (<5%) but frequent sequelae (20-30%).

There is no common consensus for choice of type, dose, and duration of the therapy of NB (Ceran *et al.,* 2011; Guven *et al.,* 2013; Hanefi *et al.,* 2009; Hatami *et al.,* 2010; Karsen *et al.,* 2012).

Monotherapy is not indicated for high risk of relapses (40-80%), therefore, the combination of two or three antibiotics (doxycycline, rifampicin, trimethoprim-sulfamethoxazole, streptomycin, ceftriaxone, ciprofloxacin) was recommended (Ceran *et al.,* 2011; Conti *et al.,* 1983; Corbel M.J. 1976; Drevets *et al.,* 2004; Karsen *et al.,* 2012).

Some Authors suggest that antibiotic treatment has to be continued until clinical improvement, normalization of the glucose ratio CSF: serum, reduction of the CSF cells <100/mm^3 and the decrease of antibody titres; mandatory is a new therapeutic cycle for occurrence of relapses (relapse rate 5-6%) (Bouza *et al.,* 1987; Ceran *et al.,* 2011; Hanefi *et al.,* 2009; Hatami *et al.,* 2010; Karsen *et al.,* 2012; Dreshaj *et al.,* 2016).

CASE REPORT

57-year-old man had a history of recurrent transient ischemic attacks (TIAs) along with the history of diplopia for one week. During the previous year, he had reported three similar episodes that were interpreted as TIAs. The episodes were characterised by numbness and weakness of the right face and upper limb along with dysarthria, each episode lasting for approximately 1 h. Five months after the first attack, the patient noticed progressive worsening of gait and balance, gradual hearing loss, tremors of both hands, right hemifacial spasm, and memory disturbances. The patient had a past medical history of hypertension that was well-controlled with medication. His daily medical therapy included acetylsalicylic acid as prophylaxis for the neurological symptoms had been ascribed to a cerebrovascular event; and, also on the basis of previous neuroimaging studies that had shown white matter abnormalities interpreted as vascular. His neurological examination at admission disclosed an ataxic and wide-based gait, positive Romberg's sign, right sixth nerve palsy, and postural and kinetic tremors in both hands. The routine blood tests were normal. Fluid attenuated inversion recovery sequences of brain magnetic resonance imaging (MRI) detected diffuse bilateral hyperintensity areas in the periventricular and subcortical white matter. These lesions did not enhance after contrast administration but showed an increase in size when compared to the previous MRI scan performed 4 months previously. A more detailed evaluation of the patient's history revealed a recent exposure to Brucella. In fact he has eaten ricotta cheese two months before the onset of the clinical presentation. The specific laboratory tests revealed an incomplete anti-brucella antibody titer of 1:640 in the serum. On the basis of this result, cerebrospinal fluid (CSF) analysis was considered mandatory. It revealed lymphocytosis, hyperproteinorrachia, hypoglycorrachia and an incomplete anti-brucella antibody titer of 1:512. The search for *M. tuberculosis* was negative as culture and molecular test. The patient was initially treated with intravenous administration of chloramphenicol and rifampicin for 2-month. Nevertheless, a brain MRI at a follow-up of two months detected in the right frontal region, the appearance of a subdural nodular lesion, surrounded by peripheral ring enhancement and a thickened and enhanced dura mater. Therefore, the therapy was switched to rifampicin (600 mg once-daily) and sulfamethoxazole-trimethoprim (160/800 mg twice-daily) orally. At a - month follow - up visit the therapy was stopped, after 5 months of second line regimen. At that time the patient showed a subtotal improvement of the neurological status complete recovery of the sixth cranial nerve palsy and of the tremor, reduction of the postural

instability and showed an improvement in his gait. No further stroke-like episodes were reported. A repeat CSF analysis detected only mild abnormalities although both CSF and blood anti-brucella antibodies were still positive. Neuroradiological follow-up documented the reduction of the subdural granuloma, but unchanged white matter lesions.

CONCLUSIONS

In 2015, 105 cases of brucellosis were reported in Italy (ECDC). Mancini et al. described the epidemiological trends and spatial distribution of human brucellosis in Italy over 13 years (1998-2010). Eighty-nine % of the 8483 cases reported, occurred in the southern regions of Campania, Sicily, Apulia and Calabria. During the study period, the annual number of notified cases decreased significantly even in the four regions mentioned above. In the sub-period 2007-2010, the average incidence rate (no. of cases/100.000 inhabitants) in Campania globally was ≤0.5 -2,5 with respect to 2,5-10 in the sub-period 1998-2000.

Conflict of interest statement

C.T. has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck Angelini and Astellas.

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