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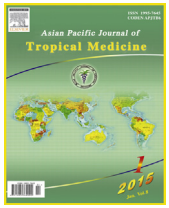

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Encephalitis with convulsive status in an immunocompetent pediatric patient caused by *Bartonella henselae*

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ABSTRACT

Cat scratch's disease caused by *Bartonella henselae*, is known to be a self-limited benign process in immunocompetent children. The association with neurologic manifestations is very uncommon especially in patient with no immunologic defects and in cases without specific treatment. A 7 years old male patient, without any immunocompromised defect, presented an atypic presentation of the cat scratch disease. The patient came to the hospital in two opportunities in a status epilepticus, in both cases the diagnosis was encephalitis by *Bartonella henselae* and the evolution with treatment was monitored with PCR (polymerase chain reaction) in cerebrospinal fluid and blood, as well as IFI (IgM, IgG) serology (indirect immunofluorescence). The patient had a favorable clinical and laboratory evolution for 6 months showing no recurrence of the disease.

1. Introduction

Bartonella henselae (B. henselae) is a gram negative *bacillus* with more frequent cases in winter and autumn. CDC reports 2.5 confirmed cases per 100000 in the USA [1]. The disease is more prevalent in children and young people which are the 80% of cases. The disease has a wide clinical spectrum, from an isolated lymphadenopathy to a systemic compromise, affecting both immunocompetent or immunodeficient patients [2,3]. The 5%–25% of the immunocompetent patients have an atypical presentation of this disease with extranodal dissemination and systemic compromise which gives many different manifestations. From this atypic cases, 1%–7% can present with neurologic complication: convulsions (40%–50%), status epilepticus (46%–80%) and other such as meningitis, encephalitis, myelitis, radiculitis and peripheral neuropathy [4] manifested more frequent in children between 7 and 12 years old.

The atypical presentation of this disease can be presented with gastrointestinal manifestations: Micro hepatosplenic abscesses and hepatitis, ocular manifestations like retinitis, choroiditis, optic neuritis and oculoglandular syndrome Parinaud (2%–17%) [6,7]. Skeletal manifestations (0.3%), osteitis, osteomyelitis, paraspinal abscess and reactive arthritis. Approximately 2% of patients develop serious and sometimes fatal complications [8].

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The clinical diagnosis is supported by epidemiological information and laboratory. At least one of the following three: Isolated regional lymphadenopathy, history of contact with cat at least for 1 year with or without primary inoculation. However, there is not always a clear history of contact or serological laboratory testing for antibodies to *B. henselae*. The CDC from Atlanta-EUA has established the diagnosis criteria with positives values of IgG higher than 1:64, specific gender 93%–96%, but it is not defined to the species [9].

For that reason, the PCR takes relevance and the diagnostic is confirming with a sensibility of 76% and a specificity of 100% in blood or cerebrospinal fluid (CSF) samples [10].

In general, the disease is self-limited in immunocompetent patients, starting with regional lymphadenopathy sometimes follow by fever for 1–3 weeks after the scratch, bite or lick of the cat and ends in 6–12 weeks with no treatment.

In the atypical presentations the pathophysiology of the encephalopathy is unknown. Different theories such as direct invasion, neurotoxin effect, vasculitis or immune response have been postulated [8,11,12]. Clinical manifestations starts after 2 weeks of infection, like headache, mental disturbance, convulsions, status epilepticus, *etc*.

2. Case

A 7 years old male from Lima, Peru, was referred from a primary attention centre to the emergency room of Edgardo Rebagliati Matins Hospital. Four hours before admission, the patient was presented with a sudden onset generalized tonic-clonic crisis lasted 5 min approximately without regaining consciousness, followed by a right hemiparesis and difficulty breathing requiring prompt ICU transfer and intubation. Once on the ICU, the patient was diagnosed with a convulsive status, to discard viral encephalitis because of the history of auto limited high temperature one week before the admission. CSF analysis and a cerebral CT scan where reported as normal. After 24 h, the patient was extubated and remaining confused and with visual hallucinations.

The first hospital auxiliary tests were as follows. Cerebrospinal fluid-CSF: Cells: 2/mL, Glucose: 91 mg/dl, Protein: 20 mg/dl; Multiple RT-Kit: Herpes simplex virus I–II, Varicella zoster, Cytomegalovirus, Epstein Barr, Herpes virus VI, VII, VIII, Enterovirus: all negative; Toxicological analysis: Negative; Brain scan: Normal; MRI of the brain: Normal; Electroencephalogram: Basal activity slow for the age; Thyroid Profile: Normal; Immunity (IgM, IgG, IgA, C3, C4): Normal; HIV: Negative; Lymphocytes CD4–CD8: Normal; Thoracic X-ray: Normal.

Next day, fever was presented again, antibiotic coverage with ceftriaxone and clindamycin for 5 d was initiated due to a suspected aspirative pneumonia. This treatment is suspended by good evolution of respiratory symptoms, less temperature and normal chest radiograph. Hallucinations persisted and were associated to orolingual involuntary movements. The patient got better so he was transferred to the General Pediatric Area where lineal injuries of a scratch on the skin of the superior and inferior members were reported. The relatives referred to have 2 cats as pets, so the empiric treatment with azithromycin 350 mg/d was started as empiric treatment for cat scratch's disease, while serology was pending. Patient was discharged due to neurological improvement.

Six days after discharged, the patient was readmitted due to a new episode of convulsive status and fever not quantified of 4 d of evolution. The results of IFI were positive for *B. henselae* and treatment with ciprofloxacin 300 mg/12 h Oral cotrimoxazole 110 mg/6 h Ev and rifampicin 450 mg/24 h Oral was initiated.

He was evaluated by the Pediatric Neurology and infectology department, who suggested to maintain Rifampicin, initiate with macrolide, a PCR amplification studies in CSF for *B. henselae*, retest for *Bartonella* serology, ophthalmology evaluation, MRI of the brain, echocardiogram, Thoracoabdominal CT-Scan and immunology studies. With treatment indicated evolves with neurological improvement.

The second hospital auxiliary tests were as follows. Anti receptor antibody N-methyl-D-aspartate: Negative; Echocardiogram: Minimal tricuspid insufficiency-Normal; Electroencephalogram: Quick diffuse activity; Ophthalmic fundus examination: Discs with slight blurring at baseline in both eyes; Visual evoked potential: Normal; Cerebrospinal fluid: Cells: 2/mL, Glucose: 44 mg/dl, Protein: 18 mg/dl; Determination of visual acuity: 20/20 both eyes, anisocoria a slight predominance of left eye; Abdominal ultrasound: Mild hepatosplenomegaly.

In the second week of treatment, he was reevaluated by the Pediatric Infectologist; for the appearance of diplopia and persistent headache. He presents an optic fundus with effacement of the optical disc in both eyes. A B-PCR study in CSF and in blood was reported as positive for *Bartonella* genus (Table 1). The normal MRI helps to exclude cerebrovascular event, metastatic disease and autoimmune encephalitis, due to the suspicious of a bacterial infection, azithromycin and rifampicin is restarted with neurological signs and symptoms in remission and normal fundoscopy.

The patient was discharge with the same antibiotic treatment and a control with PCR in blood and serology IFI IgG-IgM for BH. The PCR negative and serology was still positive BH IgG1: 64(+), IgM > 1:20(+), so the patient was advised to complete the 4 weeks of antibiotic treatment. Phenobarbital

Table 1
Treatment and monitoring laboratory.

Treatment		Tests			
		IFI		PCR	
		IgG	IgM	Blood	CSF
First hospitalization	CRO+ CLI 4 d, AZM 5 d	–	–	–	–
Second hospitalization	CIP + SXT + RIF 14 d	Positive 1:256[a]	Positive >1:20[b]	–	–
	RIF + AZM	Positive 1:64[a]	Positive <1:20[b]	Positive	Positive
Discharge	Complete RIF + AZM 14 d	–	–	Negative	–
	Control 6th Month	Negative	Negative	–	–

[a] Positive: antibodies; Negative: no antibodies; early infection: values of IgG > 0 = 1:256. [b] Positive: antibodies; Negative: no antibodies; early infection: values of IgG > 0 = 1:120.

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was indicated as seizure prophylaxis and was tapered off in 5 months after pediatric infectiologist and neurologist evaluation.

Currently the patient is asymptomatic with negative IFI serology, negative IgG in the 6th moth of tracing.

3. Discussion

B. henselae is the etiological agent of the cat scratch's disease. The history of the scratch or bite of the cat is a useful criteria for the diagnosis, however it is not always reported [8]. As in this case, the diagnosis was delayed due to the lack of awareness regarding the presence of the skin lesion and the epidemiological information.

Most of the patients with CSD present with fever and lymphadenopathy near the skin lesion and with a history of contact with cats. On the other hand, atypical clinical manifestations are very rare with a variable presentation including: prolonged fever of unknown origin and hepatosplenic, ocular and neurological manifestations [13]. Neurological symptoms are rare specially in immunocompetent patients [4].

The diagnosis of the *B. henselae* as the etiological agent of CSD is not easy done due to the limited resources which are not available in all the medical centers and as well as the difficult isolation of the bacteria [13,14]. For that reason, most of the times the diagnosis is clinical without etiology confirmation. Another diagnosis difficulty is that in the children with encephalitis are suspected to have a viral or bacterial etiology different from bartonelosis [15].

Our patient without any previous pathological event is admitted to the IUC twice with encephalitis and convulsive status, where it was done multiple testing discarding viral and autoimmune encephalitis besides negative immunodeficiency studies. In front of the suspicious of CSD, with a wider history of contact and the good neurologic evolution with treatment. The patient is discharge after 9 d with an empiric treatment of azithromycin and IFI serology of *B. henselae* as outpatient. In addition, some studies indicated that the benefit of one or other antibiotic therapy is not confirmed at all, especially in immunocompetent children 1 as our case. In fact there is no an ideal treatment that was stablished already [16]. Additionally, studies may differ in the recommendations of antibiotic treatment for bartonellosis, especially in immunocompetente hosts as our patient [16].

Nevertheless, our patient in his fifth day of treatment as an outpatient with azithromycin, was readmitted in a convulsive status with signs of encephalitis and the diagnosis was confirmed with positive serology IgM-IgG for *B. henselae*. And ciprofloxacin 21 mg/kg/24 h, trimethoprim-sulfametoxazol 16 mg/kg/24 h, rifampicin 14 mg/kg/24 h for 14 d where added in the ICU. The therapy was decided after bacterial antibiotic resistance studies to macrolides, fluoroquinolones, tetracyclines, rifampicin, and trimethoprim-sulfamethoxazole, being the most effective rifampicin 87%, ciprofloxacin 84%, intravenous gentamicin 73% and TMP/SMX 58%. However, there is not a consensus regarding the ideal therapeutic regimen [16,17].

It is proposed again a therapy considering the mechanisms of the *B. henselae* against de CNS which are persistent bacterial load in CSF, autoimmunity, critical effect of the toxin [8,12,18]. Facing the readmission and persistent symptomatology and suspicious ocular impairment [6] we must have an etiology diagnosis based on persistent of bacterial activity in the CSF in an immunocompetent child, for that reason we make PCR, blood and CSF serology with combine treatments. The utility of the molecular techniques (PCR) for the diagnosis of encephalitis due to B.H. and other atypical etiologies gains special attention in the need to establish a bacterial load in CSF and blood specimen [10].

To date, the recommended treatment for BH is rifampicin with azithromycin. Different authors use rifampicin in their multiple antibiotics therapy [18,19]. Because of this penetration into the CSF and recommended to be associated with a macrolides in children, especially if recurrences [8,20]. However, there is a lack of evidence regarding the treatment in immunocompetent patients with atypical presentation involving neurological manifestations, in whom severe sequelae and fatal cases have been reported [8].

Our patient after 6 months of treatment reported has no recurrence, he is asymptomatic without anti convulsive therapy and with negative IgM-IgG values for BH in his last control. Regarding the positive serology in 1:16 or greater, which usually indicates acute illness, it has been reported that can remain positive in up to 3 months in the 50% of cases. The IgM antibodies are not usually detected and a negative result does not rule out the disease. Higher IgG levels, greater than 1:256 is evidence of actual or previous infection of *Bartonella*. IgG levels also fall and 75% are negative after a year. Evidence shows that some patients never reach values of detectable antibodies. For that reason, disadvantages of the serologic diagnosis include variable sensitivity and specificity reported values and the inability to distinguish between active or previous infection [21].

Conflict of interest statement

We declare that we have no conflict of interest.

Uncited reference

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