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COMMENTARY

A traveler with neurobrucellosis

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Summary An Indian traveler developed fever and neurological symptoms after a visit to East Africa. He was treated with suramin, melarsoprol and prednisolone for presumed East African trypanosomiasis. His condition deteriorated and cerebral lesions developed. Neurobrucellosis was diagnosed. Combination antibiotic therapy led to gradual clinical improvement and regression of the brain lesions. Misdiagnosis of East African trypanosomiasis followed by treatment with potentially lethal medication should be avoided by not relying on insufficient evidence during the diagnostic process.

Introduction

International travel has increased dramatically in the last decade. This increase, together with the fact that many exotic places are now less than 48 h away from any spot on the planet, has led to a rise in travel-related medical problems. Fever is a common presenting symptom in travelers. The causes are well studied in Western tourists returning from exotic places, but less is known about fever in intercontinental travelers from India.[1] In this article, a case of neurobrucellosis is described in an Indian traveler who was initially suspected to have East African trypanosomiasis.

Case report

A 43-year-old Indian man was referred for a second opinion. Five weeks earlier, he had traveled from India to East Africa for business, staying only in major towns. He had also visited Cyprus, Oman, Yemen, Syria and Sri Lanka in the past 6 months. Three days after arriving in Tanzania, he developed fever and general malaise (day 1 of illness). His left ankle became red and swollen; he had no recall of an insect bite. The next day in Uganda, he took oral flucloxacillin 500 mg q6 and diclophenac. On day 4, he arrived in Nairobi with high fever, epistaxis and coarse tremor of both hands. A quantitative buffy coat test (QBC) performed in Nairobi was reported positive for trypanosomes (''scanty parasites seen''). The results were given by telephone while the patient was boarding his flight back to New Delhi. In India, trypanosomiasis could not be confirmed on thick

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and thin blood films nor with polymerase chain reaction (PCR) on blood. On day 9 he was still febrile despite 8 days of flucloxacillin followed by 5 days of ceftriaxone. The ankle was still red and swollen and the tremor had increased. He developed leukopenia (2800/μL), thrombocytopenia (93,000/μL), and moderately elevated transaminases (Table 1). Hepatosplenomegaly was noted on abdominal ultrasound. A lumbar punction was performed and showed an elevated protein level (Table 1). The cerebrospinal fluid was clear without cells, no parasites were seen, and cultures remained negative. Serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) was negative, as was a thick smear for malaria, Widal test and blood cultures. Chest X-ray and transthoracic echocardiography were normal. On day 9 magnetic resonance imaging (MRI) of the brain was normal apart from slight enhancement of the meninges. In view of the worsening clinical picture and the positive parasitological report reported from Nairobi, it was decided to treat the patient as East African trypanosomiasis without confirmation of the diagnosis. He was given suramin 0.5 g and 1 g on day 12 and 13 respectively, together with prednisolone 50 mg q24. This was followed by melarsoprol 180 mg daily on 3 consecutive days, repeated once after one week. Two days after the start of suramin with prednisolone, the fever dropped from 39—40 °C to 37.1—37.5 °C. A second MRI of the brain on day 15 showed four new lesions in the white matter.

The patient was referred 5 weeks after onset of his illness. On admission he was afebrile (37.1 °C), blood pressure was 120/80 mmHg and pulse rate 95/min. A coarse tremor of both hands interfered with his ability to eat. He had gait difficulties and slurred speech. His left ankle showed mild erythema and dry skin without edema. He had an irritated antecubal IV melarsoprol-injection site. Pancytopenia and mildly elevated transaminases were present (Table 1). Inflammatory parameters were surprisingly moderate. Serology was negative for HIV, hepatitis A virus (HAV), HBV, HCV, syphilis, leptospirosis, *Schistosoma, Rickettsia, Coxiella burnetii, Borrelia, Plasmodium* and *Leishmania*. Repeated thick smear, urine analysis and fecal examination for parasites were negative as well as assays for antinuclear factor, lupus anticoagulant and thyroid stimulating hormone (TSH). Protein electrophoresis showed beta-gamma bridging. Tests for trypanosomiasis were all negative, including thick and thin blood smears, serology (card agglutination test [CATT] and immunofluorescent test), two buffy coats, two tests with the miniature anion exchange centrifugation technique (mAECT) and two Woo-techniques. Chest X-ray was normal. Ultrasonography of the abdomen confirmed hepatosplenomegaly (liver 17.5 cm; spleen 13.5 cm). MRI of the brain just after his arrival in Belgium showed 4 lesions in the white matter, the largest left temporoparietal with apparent penetration of the blood brain barrier (Fig. 1). The lesions showed a prolonged T2-time and did not enhance with gadolinium. Bone marrow and liver biopsies showed ill-defined granulomas. No micro-organisms were seen. Bone marrow cultures remained negative. A tuberculin skin test was non-reactive. Five days after his referral blood cultures grew *Brucella melitensis* biovar 3. The Rose Bengal test and Wright test were also strongly positive (*Brucella abortus* 1/2560, *B. melitensis* 1/640). Bacterial cultures and serology for *Brucella* in cerebrospinal fluid were negative. Transoesophageal echocardiography and fundoscopy were normal. Oral rifampicine 900 mg/day, doxycyclin 200 mg/day and IV gentamicin 5 mg/kg/day were started. After two weeks gentamicin was replaced by cotrimoxazole 800/160 mg b.i.d. After 7 days the patient became afebrile and felt much better. He could eat and speak normally. Liver span, spleen, full blood count, C-reactive protein (CRP) and liver tests returned to normal (Table 1). The hand tremor gradually improved. Two weeks starting his treatment, MRI of the brain showed marked reduction of all lesions. The patient returned to India and continued his treatment for 6 months.

Discussion

The combination of this patient's clinical signs and recent travel raised the possibility of East African trypanosomiasis. Since the patient also visited Uganda, a country where both

Table 1 Evolution of hematological and biochemical parameters, as well as cerebrospinal fluid indices.

Peripheral blood	Day 11 of illness	Day 39	Day 49
Hb (g/dl)	14.4	12.8	13.2
WBCs (/μl)	4.4×10^3	2.8×10^3	5.4×10^3
Platelets (/μl)	161×10^3	97×10^3	146×10^3
CRP (mg/dl)	N/A	0.7	<0.32
ESR (mm/h)	40	43	42
LDH (U/L)	N/A	601	508
Alc. Phosph. (U/dl)	1016	261	199
AST/ALT (U/dl)	191/190	80/101	74/84
Cerebrospinal fluid			
WBCs (/μl)	0	8	10
RBCs (/μl)	0	0	0
Gram stain	Neg	Neg	Neg
Culture	Neg	Neg	Neg
Protein (mg/dl)	93	98	62
Glycorrachia/glycemia (mg/dl)	57/101 (56.4%)	66/111 (59.5%)	48/92 (52.2%)

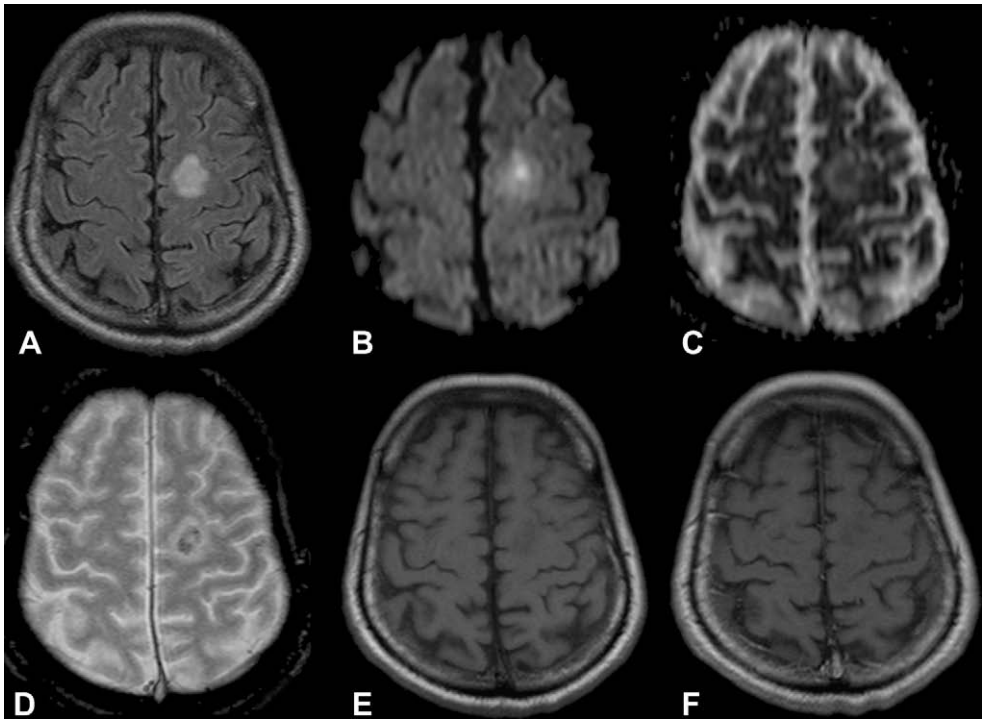

Figure 1 MRI of the brain. MRI of the brain performed on day 15 demonstrates areas of high signal intensity on FLAIR (A) and T2-weighted images (not shown) within the brain. The center of the lesions is hyperintense on diffusion-weighted imaging (B) and hypointense on apparent diffusion coefficient (ADC) map (C) indicating restricted diffusion. Some vasogenic edema may be observed. Gradient echo T2*-weighted images (D) display areas of low signal intensity, indicating the presence of calcification, iron, or micro-hemorrhagic components. The lesion is isointense with the cortical gray matter on T1-weighted sequences (E) and no enhancement is observed after gadolinium-injection (F). No leptomeningeal enhancement is present.

forms of African trypanosomiasis exist, even the possibility of the West African form was briefly entertained, as was the possibility of *Trypanosoma evansi* or *Trypanosoma lewisi* infection.[2,3] However, the onset of fever on the 3rd day after arriving in Tanzania, the absence of an insect bite, nor visits outside the urban area made African trypanosomiasis unlikely, even with a single positive-reported QBC test performed seven days after his arrival in Africa (day 4 of his illness). The cellulitis on his leg might initially be mistaken for an inoculation chancre, but there was no ulcer. In retrospect, the report of a single scantily positive QBC test in Nairobi was not enough to justify starting a potentially lethal treatment with arsenicals without further confirmation. A possibility of a false positive test result should have taken into account. One should avoid to take dramatic action by not relying on insufficient evidence in the diagnostic process. Melarsoprol encephalopathy appears in about 3—10% of patients, and has a mortality rate of around 50%.[4,5] It is also known to occur in non-infected people.[6] The masking of the fever under the immunosuppressive effect of steroids combined with suramin delayed the final diagnosis. Once melarsoprol was given, the patient's neurological situation deteriorated. This left a wide differential diagnosis including trypanosomiasis non-responding to treatment, melarsoprol-toxicity, or another infectious or inflammatory febrile encephalopathy including tuberculosis. Neurolues and Q-fever were ruled out. Viral encephalitis and rabies were deemed to be unlikely because of the protracted course. Metabolic encephalopathy in Wilson's disease can result in hepatosplenomegaly and neurological symptoms, but is not accompanied by fever or inflammatory signs. The positive hemocultures, positive Rose—Bengal test, granulomas in the bone marrow, and the improvement of the neurological symptoms after starting anti-brucellosis antibiotics favoured the diagnosis of neurobrucellosis. Bone marrow culture remained negative, which was surprising in retrospect, since *Brucella* sp. usually grow well in such cultures. This negative result remains unexplained, although the previous administration of antibiotics might have played a role. An additional neurotoxic effect of melarsoprol could not be ruled out, although arsenic encephalopathy causes diffuse lesions with hemorrhagic encephalitis and cerebral edema.[7,8] However, there are no large published series of MRI studies of the brain in African trypanosomiasis or melarsoprol encephalopathy.

Clinical diagnosis of brucellosis is difficult, since its manifestations are protean. Fever, arthralgia or arthritis, constitutional symptoms and hepatosplenomegaly are among the more common symptoms. Neurological involvement is rare and includes peripheral neuropathies and central nervous system symptoms.[9,10] An electromyography was not performed. On MRI studies of neurobrucellosis, findings are classified either as normal, inflammatory, white matter changes or vascular changes.[11,12] It is important to note that not all blood culture media support growth of *Brucella*. Once the diagnosis of brucellosis was clear, the patient told us he regularly consumed home-made cottage cheese, in India as well as during his travels in the Middle East. This was most likely the source of his infection. His

case provides a warning against starting potentially lethal medication if clinical suspicion of African trypanosomiasis is insufficient. It also illustrates the need for additional medical training in recognizing exotic infections. An easy to use serological test for East African trypanosomiasis, analogue to the CATT-test for West African trypanosomiasis, would be welcome.

Conflict of interest

There are no competing interests to declare.

Funding

This does not concern a research case, but a case report from daily practice. The cost of the trypanosomiasis tests was borne by the Institute of Tropical medicine, Antwerp, Belgium.

Ethical statement

It was considered that no specific ethical approval was needed for this case report.

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