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Case Report

NEUROBRUCELLOSIS- A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT
Neurobrucellosis is a rare form of systemic brucellosis, a disease acquired through ingestion of unpasteurized dairy products, which may manifest as stroke, encephalitis, meningitis, or psychiatric disorders. Presently there is no known report of neurobrucellosis in Nigeria, although consumption of unpasteurized dairy products is not uncommon in this country. In this report we present a 28 year old spinster with history of significant ingestion of unpasteurized cow milk and brucellosis of the brain diagnosed in our centre through brain magnetic resonance imagining (MRI) and brucella antigen agglutination test. Because of the indolent nature of brucellosis infection, it should be suspected in individuals with pyrexia of unknown origin so that early detection and treatment could prevent long-term sequelae such as focal neurologic deficits, hydrocephalus and psychiatric illness.

Key Words: Antigen agglutination test, Brucella, neurobrucellosis, unpasteurized dairy products.

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INTRODUCTION
Brucellosis[1], also called Malta fever /Mediterranean fever/ Gibraltar fever/Cyprus fever /remittent/undulant fever from the intermittent nature of the fever, is a zoonotic disease transmitted to humans through ingestion of untreated milk, milk products or by contact with infected animals, animal discharges (urine, stool, vaginal and products of conception), meat or bone marrow through the skin, conjunctiva or lungs. Rarely transmission has occurred via sex or to babies via placenta or breast milk[2]. Human disease can be caused by any of four species [3];-Brucella melitensis acquired primarily from goats, sheep and camels; Brucella abortus from cattle; Brucella suis from pigs/hogs; and Brucella canis from dogs.

These organisms migrate to the regional lymph nodes, thence by hematogenous spread to other organs including the nervous system. It is difficult to know how frequently the nervous system is affected, because of nonspecificity of the infection, difficulties in diagnosis and variability in reporting such complications [4]. As there is no known report of this condition from the African continent, we decided, therefore, to report this case diagnosed in our centre through brain magnetic resonance imagining (MRI) and brucella antigen agglutination test.

CASE REPORT
N.D, a 28 year old spinster was referred to us from Jos on the 6th of June 2007 with a month history of left hip pain, high grade, intermittent fever with chills and rigors, generalized and throbbing headache, and repeated episodes of projectile vomiting, one week of abnormal behavior, focal seizures and weakness of the left limbs and, five days later of loss of consciousness. There was no photophobia, neck stiffness, night sweats, weight loss or contact with a TB case, although she ingested unpasteurized fresh cow milk. She had no history of diabetics, hypertension, sickle cell disease, high risk sexual behavior, or illicit drug use, alcohol consumption or cigarette smoking and no recent travel outside Nigeria. On presentation, she was toxic looking, febrile (39.4^0C), diaphoretic, dehydrated, moderately pale, anicteric with no significant lymphadenopathy. Glasgow coma scale (GCS) was 6/15. There were no signs of meningeal irritations and pupils were normal in size and reacted briskly to bright pen torch light. The eyes roved spontaneously and conjugately. There were bilateral papilloedema on fundoscopy; left supranuclear facial nerve palsy and an ipsilateral spastic hemiplegia. Other systems were normal. A provisional diagnosis of tuberculous encephalitis with right hemispheric tuberculomas was made, with a differential diagnosis of brucella encephalitis and? toxoplasmosis.

Brain T1 weighted MRI done on admission showed multiple hyper intense lesions in the thalami (the right being more affected than the left), the left basal ganglia and cerebral cortex, with periventricular oedema and mild communicating hydrocephalus. There was no ring enhancing lesion seen (Figure 1).

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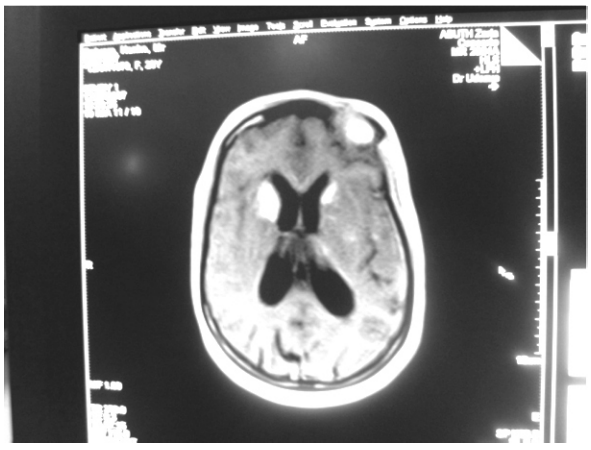
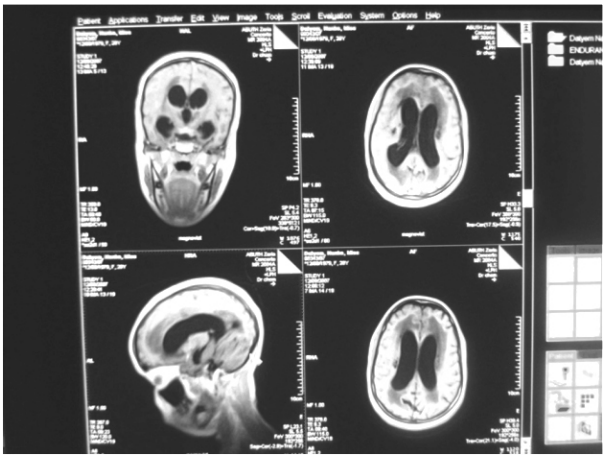
Three cultured blood specimens yielded no growth. Urine and stool cultures also yielded no growth. Packed cell volume was 27%, with total white blood count of 6.8X109/L, (made up of 84% neutrophils and 16% lymphocytes).The erythrocyte sedimentation rate (ESR) was 10mm/hour, Mantoux skin reaction was negative, and HIV- 1& 2 were sero-negative. Serum urea, uric acid, electrolytes, creatinine, calcium, phosphate and proteins were all within normal limits. Random blood sugar was 5.6mmol/l. Liver transaminases [aspartate transaminase of 90 i.u/L (normal range 5-22), alanine transaminase of 102IU/L (normal range 16-40)] were raised, while alkaline phosphatase and total bilirubin levels were normal. Chest x-rays, electrocardiography and echocardiography were essentially normal. Brucella abortus agglutinin test yielded a titre of 1:128. These investigation results pointed more towards neurobrucellosis than tuberculosis, and so anti-brucellosis therapy was instituted with intramuscular (IM) Streptomycin 1g daily, caps Rifampicin 600 mg daily and Doxycycline 100 mg b.d through a naso-gastric tube, which also served for feeding. She was also put on IV dexamethasone 8mg 6hourly, IV normal saline 3-6 litres/day. Seizures were controlled with Phenytoin 300 mg daily P.O., and two tablets of artesunate/amodiaquine daily were given for 3 days (after a result of +1 plasmodium falciparum parasitemia was received). Four weeks later, pyrexia began to subside with more apyrexic intervals, GCS improved to 10/15 but focal deficits persisted.
Repeat brain T1 weighted MRI revealed resolution of previous hyper intense lesions in the thalami, basal ganglia and cerebral cortex, but the size of the communicating hydrocephalus increased (figure 2). Repeat brucella antigen agglutination test yielded a titre of 1:64.

Figure 1:**T1 Weighted MRI of Brain showing Hyper-intense lesions in the thalami (right > left), right basal ganglia and cerebral cortex.**



The patient was continued on Doxycycline 100 mg b.d PO, Rifampicin 600 mg PO and Streptomycin 1g IM . Dexamethasone was stopped. She had regular physiotherapy and adequate skin, bladder and bowel care. At the 8th weeks, her clinical condition remained stable, fever stopped, but GCS and focal deficits remained unchanged. Repeat brucella antigen agglutination test yielded a titre of 1:16.She was subsequently transferred to a neurosurgical facility because of worsening hydrocephalus.

Figure 2**: T1 Weighted MRI of Brain showing resolution of previous hyper-intense lesions and severe communicating hydrocephalus.**



DISCUSSION

The global incidence of human brucellosis is not known because of the variable quality of disease reporting and notification system in many countries. As a result, it is usually underreported, although over 500,000 cases are reported yearly from 100 countries[4]. Even in Europe and United States of America with stringent disease surveillance and report systems, the true incidence of this disease is not known [5, 6], although some countries in Europe are reported to be free of brucellosis [6]. In Nigeria with a significant population of herdsmen, no literature on this condition is available to these authors.
Neurobrucellosis is uncommon, developing in <5% of patients with Brucella infection , and producing diverse neurological syndromes[7], even in the same patient [8], the most frequent being diffused or localized meningitis [9] or meningoencephalitis[10] which could be acute, subacute, relapsing or chronic. Less than 50% of patients may exhibit meningeal signs. Clinical features may include alteration of consciousness, psychiatric disturbances, long tract signs, convulsions and focal neurologic deficits especially in the presence of multiple cerebral lesions. Involvement of cranial nerves II, III, IV and

VI in basal meningitis may lead to papillitis, papilloedema, retrobulbar neuritis, optic atrophy and opthalmoplegia. These features may be indistinguishable from those of tuberculous or fungal meningitis and CSF findings are similar[11,12]. It is therefore not surprising that a diagnosis of tuberculosis was considered first in our patient as tuberculosis is commoner in our environment than brucellosis. The infection[12] may also produce subarachnoid hemorrhages from ruptured mycotic aneurysm; embolic stroke from emboli from brucella endocarditis. Thrombotic strokes can be caused by vasculitic changes in the cerebral vessels and this phenomenon must be responsible for the residual neurological deficit seen in this patient.

Mass lesions within the brain parenchyma are extremely uncommon but have been documented radiologically and pathologically[13]. Lower thoracic and lumbar myelopathy, acute and chronic may result from several different mechanisms such as acute transverse myelitis, spinal cord infarction, adhesive arachnoiditis, and compression from epidural abscess, brucella spondylitis, and/or vertebral erosion and collapse. Diagnostic confusion may occur with lumbar disc protrusion and tuberculous spondylitis. Cervico-brachial plexopathies, lumbo-sacral plexo-radiculopathies may occur as part of inflammatory processes. Mononeuritis multiplex and peripheral neuropathies have been described[7]. Brucellosis as a cause of psychiatric illness is easily missed especially if the patient has no overt physical abnormality[12]. All this diverse manifestations can lead to confusion and delay in diagnosis and may lead to diffulties in differentiating this condition from other chronic infections like tuberculosis and syphilis [15].

Antibody against brucella may be demonstrated in serum and cerebrospinal fluid (CSF) by enzyme linked immuno-sorbant assay (ELISA), standard tube agglutination (SAT), the 2-mercaptoethanol agglutination test and Coombs' test using Brucella abortus antigens, which cross- react with Brucella melitensis and Brucella suis but not with Brucella canis (which has no approved commercial kits). No single titre of brucella antibodies is diagnostic. However, in endemic areas, a titre of 1:320 or 1:640 is significant while a titre above 1:80 in non endemic areas is considered significant in serum or CSF; although CSF titres are lower than those of the serum. In endemic areas, a high titre in the absence of symptoms should be followed by re-evaluation in 2-4 weeks and a further rise in titre sought[14].

Cultures of blood and bone marrow are positive in 50-70% of cases, but could last up to 6 weeks before growth of organism is seen. Subcultures could be prepared on special media or duplicate blood agar plates (with or without 10% carbon dioxide). Radiological abnormalities are nonspecific and computerized tomographic (CT) appearances of neurobrucellosis are similar to those of tuberculosis and other granulomatous meningitides/encephalitides. However, MRI is modality of choice as it shows diffuse hyper intense signals in affected nuclei.

The major problem in antibiotic treatment is the intracellular location of the organism[15]. There is no unanimity of opinion regarding the optimal regimen. Most authorities recommend the use of doxycycline 100 mg PO BID in combination with two or more other drugs (Rifampicin 600-900 mg PO QD/ streptomycin 1 g IM QD or trimethoprim-sulfamethoxazole 960 mg) for one to nine months till serum /CSF antibody titres are reduced to a minimum. Other regimens include: Netilmicin 2 mg/kg 12 hourly IM or Gentamicin 3-5 mg/kg /day in divided doses 8 hourly plus Doxycycline 100 mg BID. Benefits of corticosteroids have not been demonstrated in clinical trials. Mortality is low and the cause of death may not always be related to brucellosis[15]. All patients should be kept under review for at least a year following completion of antibiotic course when the serum agglutinins should have fallen to normal level. Because of the indolent nature of this infection, early detection and treatment could prevent long-term neurologic complications of chronic intracranial inflammatory process such as hydrocephalus as occurred in our patient.

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