

# Progressive meningoencephalitis in a Sudanese immigrant

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## Clinical record

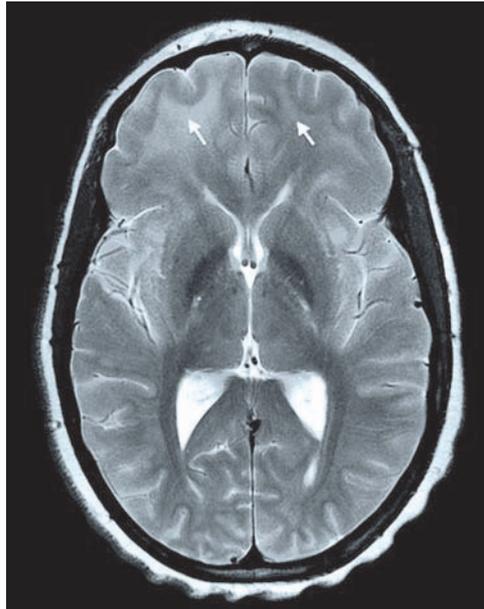
A 24-year-old woman presented to hospital in May 2009 after two generalised seizures with focal motor onset involving the right arm and leg. She had a 2-month history of intermittent frontal headaches and twitching of the right hand that did not interfere with usual activities. Her family had noticed she had lost weight. The patient was originally from the Eastern Equatoria province in southern Sudan and spent 12 years in a Ugandan refugee camp before migrating to Australia in 2007 with her family. Her only significant past medical history was malaria. Her family were in good health.

On admission, the patient was hypothermic (temperature, 35.7°C), with a Glasgow Coma Scale score of 6, and gaze deviation to the left. Initial investigations showed hypochromic, microcytic anaemia (haemoglobin concentration, 100 g/L, reference range [RR], 115–160 g/L; mean cell volume, 65 fL, RR, 78–101 fL; and mean cell haemoglobin, 20 pg/cell, RR, 25–35 pg/cell), hyponatraemia (132 mmol/L; RR, 135–147 mmol/L), and raised serum protein level (109 g/L; RR, 60–84 g/L). Results of computed axial tomography of the brain with contrast and chest x-ray were unremarkable. Cerebrospinal fluid (CSF) contained polymorphonuclear leukocytes ( $45 \times 10^6/L$ ), mononuclear cells ( $168 \times 10^6/L$ ), red blood cells ( $23 \times 10^6/L$ ), protein (0.88 g/L) and glucose (2.5 mmol/L). No organisms were seen on Gram stain.

Persistent status epilepticus necessitated treatment with loading doses of phenytoin, sedation and intubation. Magnetic resonance imaging (MRI) of the brain showed extensive areas of uniform high signal intensity within the supratentorial white matter and mild meningeal enhancement (Box 1). Meningoencephalitis was diagnosed, and the patient was treated with ceftriaxone and aciclovir. Based on history, presentation and cerebrospinal fluid findings, she was also given isoniazid, rifampicin, ethambutol, pyrazinamide, pyridoxine and dexamethasone for suspected tuberculous meningoencephalitis. Multiple investigations for bacterial, viral and fungal pathogens, including serological tests for HIV, and polymerase chain reaction (PCR) tests and culture for *Mycobacterium tuberculosis*, gave negative results (Box 2).

The patient was extubated on Day 4, and her condition improved, with no further seizures, although periods of fluctuating drowsiness and confusion were noted. Electroencephalography showed generalised slowing consistent with diffuse cerebral dysfunction. To clarify the diagnosis, lumbar puncture was repeated; CSF showed polymorphonuclear leukocytes,  $0 \times 10^6/L$ ; mononuclear cells,  $141 \times 10^6/L$ ; protein, 0.52 g/L; and glucose, 2.0 mmol/L; but was again Gram stain-negative. Investigations for autoimmune and malignant disease, as

## 1 Magnetic resonance image of the brain 17 days after presentation



An axial T2-weighted magnetic resonance image at the level of the basal ganglia showed symmetrical high signal intensity in the white matter, particularly in the centrum semi-ovale (subcortical white matter) (arrowed).

well as mitochondrial disorders and metabolic leukodystrophies gave negative results (Box 2).

Cervical lymphadenopathy was identified in the posterior cervical triangle, and examination of a fine needle aspirate suggested reactive lymphadenitis. A subsequent biopsy showed relatively preserved nodal architecture with reactive follicles, and no evidence of granulomas or malignancy. PCR testing of the biopsy specimen for *M. tuberculosis* and culture gave negative results.

In view of the apparent clinical response to treatment, tuberculous meningoencephalitis was considered the most likely diagnosis, despite the negative results on investigation and brain MRI. The patient was discharged on Day 36, with continuing treatment with the anticonvulsant levetiracetam, antituberculous therapy and dexamethasone (4 mg tapering by 1 mg weekly).

The patient re-presented 2 weeks later with increasing confusion, somnolence, gait unsteadiness and worsening bilateral tremor, and was re-admitted. Repeat MRI of the brain with gadolinium contrast showed progression of the diffuse subcortical and deep white matter abnormalities observed on previous MRI, with extension

into the midbrain and pons. Treatment was begun with methylprednisolone (4 mg daily), and antituberculous therapy was discontinued.

A diagnosis of West African trypanosomiasis was considered, but peripheral blood and lymph node tissue were negative for trypanosomes; lumbar puncture was not performed because of concern about increased intracranial pressure. Because of a rapid deterioration in the patient's condition and the continuing uncertainty over the diagnosis, a stereotactic brain biopsy was performed. Histological examination of the biopsy specimen showed meningoencephalitis with Mott (morula) cells (Box 3A), suggesting human African trypanosomiasis (HAT). Review of the previous CSF cytology specimens also revealed Mott cells (Box 3B), which had not been recognised initially. Indirect haemagglutination tests of serum for HAT-specific antibodies gave positive results, with a titre of 1:4096.

Treatment with intravenous pentamidine (200 mg daily) was begun 2 months after the patient's first presentation and was continued for 4 days pending the arrival of eflornithine provided by the World Health Organization. The patient regained consciousness after pentamidine treatment began, and her condition improved dramatically with a 14-day course of intravenous eflornithine (5 g four times daily). Corticosteroid therapy was tapered and ceased.

She was discharged to a rehabilitation unit, able to walk independently and undertake basic activities of daily living, but requiring ongoing help with executive functioning. After discharge, she

returned to her family and community life. She had a residual hand tremor but continued to show steady improvement in level of functioning, mentation and social interactions. At 3-month follow-up, she remained well, but repeat lumbar puncture revealed persisting CSF lymphocytosis.

**2 Summary of investigations undertaken with negative results\***

**Infectious diseases screen**

**Viruses.** Cytomegalovirus (IgM, IgG); Epstein–Barr virus (IgM, IgG, PCR), herpes simplex virus and human herpes virus 6 (PCR), adenovirus, influenza A and B viruses, parainfluenza virus, and respiratory syncytial virus (DIF), and hepatitis A, B and C and HIV (serology).

**Bacteria.** *Brucella abortus* (serum agglutination titre), meningococcus (PCR), mycobacterium (PCR, culture), mycoplasma (PCR), syphilis (serology), streptococcal antigen, rapid screen for bacterial antigens, and blood, urine, cerebrospinal fluid, sputum and stool cultures.

**Parasites.** Blood parasite screen (including malaria), cryptococcal antigen, schistosomiasis (IgG) and toxoplasma (IgM, IgG).

**Toxicology screen:** Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, methadone, opiates.

**Metabolic screen:** Cerebrospinal fluid pyruvate, lysosomal enzymes and very long chain fatty acids.

**Immune screen:** Anticardiolipin antibody, anti-double stranded DNA, antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigen antibodies, anti-Purkinje cell antibody, antineuronal antibody, anti-neuromyelitis optica antibody, complement levels, cryoglobulins, lupus anticoagulant,  $\beta_2$ -glycoprotein,  $\beta_2$ -microglobulin, thyroglobulin antibody, thyroperoxidase antibody and oligoclonal bands.

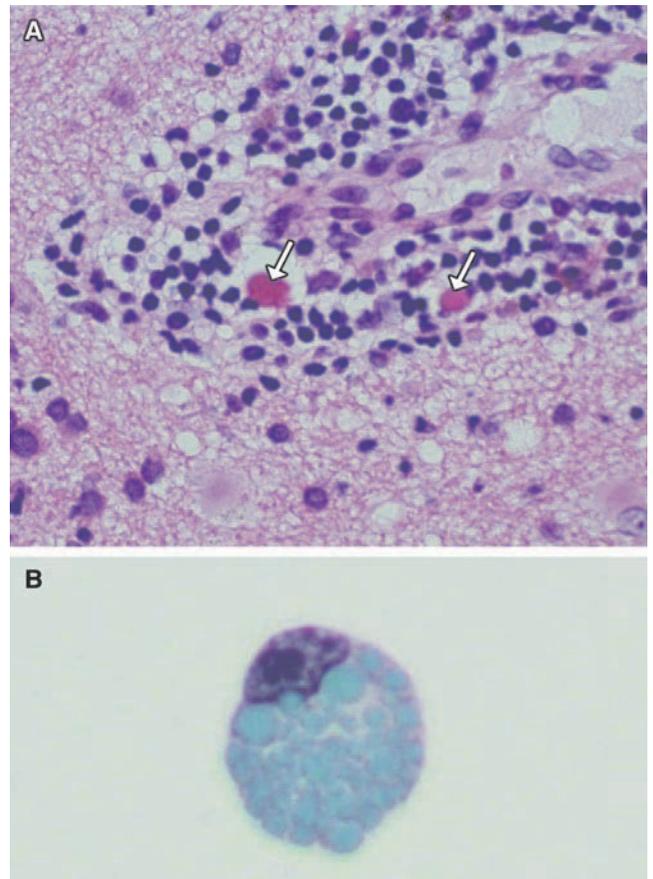
**Oncology screen:**  $\alpha$ -Fetoprotein, tumour markers Ca 125 and Ca 19-9, flow cytometry for cell markers, and serum electrophoretogram/immunoelectrophoretogram.

**Other tests:** Serum cortisol,  $\beta$ -human choriogonadotropin, iron studies, thyroid function, vitamin D level and vitamin B<sub>12</sub> and folate studies.

PCR = polymerase chain reaction. DIF = direct immunofluorescence.

\* Tests are categorised for easy reference but were not necessarily performed in the order shown, rather on different occasions as clinically indicated. For example, investigations for toxoplasma and cryptococcus were performed shortly after the patient was first admitted, but those for schistosomiasis not until her second admission, almost concurrently with trypanosomiasis testing. ♦

**3 Mott cells in the patient's brain and cerebrospinal fluid**



**A.** White matter from a brain biopsy specimen taken during the patient's second admission showed perivascular inflammatory infiltrates composed of lymphocytes and plasma cells, including Mott (morula) cells (arrows). The cytoplasm of Mott cells contained brightly staining eosinophilic immunoglobulins (high-power magnification, haematoxylin and eosin stain).

**B.** Review of the CSF specimens taken at presentation showed Mott (morula) cells with large Russell body inclusions (blue-staining globules), representing immunoglobulins (original magnification,  $\times 400$ ; Papanicalou stain). ♦

**H**uman African trypanosomiasis (HAT or sleeping sickness) is a significant cause of morbidity and mortality in parts of Africa but is rarely seen in Australia. Lack of awareness of this disease among Australian physicians means it may be easily misdiagnosed, delaying timely treatment and resulting in inadvertent adverse outcomes.

HAT is caused by the flagellated protozoan *Trypanosoma brucei*. Two subspecies cause human disease: *T. brucei rhodesiense*, which is found only in east Africa and causes an acute, fulminant illness lasting weeks to months (East African HAT); and *T. brucei gambiense*, which is found in western, central and parts of east Africa, and causes an indolent, chronic infection that may last many months to years (West African HAT).<sup>1</sup> The fulminant course of *T. b. rhodesiense* illness means it is the

form more frequently diagnosed outside Africa, in returned travellers.

Infection occurs through injection of saliva containing trypanosomes from the bite of the tsetse fly, and a local skin reaction or chancre may follow. The infection follows two stages. The early (haemolympathic) stage results from proliferation of parasites in the blood and lymph and presents with headache, fever, malaise, anorexia, anaemia and lymphadenopathy. The late (meningoencephalitis) stage occurs when trypanosomes invade the central nervous system (CNS), causing a range of neurological manifestations including psychiatric changes. Inversion of the sleep–wake cycle is common, resulting in daytime somnolence and nocturnal insomnia. Without treatment, CNS disease eventually results in coma and death.

Our patient probably became infected in Uganda, where both subspecies of trypanosome are known to circulate.<sup>2</sup> In retrospect, the initial improvement in her condition was most likely a response to corticosteroid treatment, and the subsequent regression coincided with a reduction in the corticosteroid dose. Cervical lymphadenopathy in the posterior triangle was noted at initial presentation but was recognised only during her second admission as a classic feature of *T. b. gambiense* disease (the Winterbottom sign<sup>3</sup>).

Detection of trypanosomes in the CSF, blood or lymph tissue remains the diagnostic “gold standard”. However, methods of parasite detection vary in sensitivity, and the cyclical nature of parasitaemia means parasites are seldom detected in blood, especially in *T. b. gambiense* disease,<sup>4</sup> although detected more often in CSF.<sup>5</sup> We were not able to demonstrate trypanosomes in whole blood, lymph node tissue or CSF. In the absence of demonstrable parasites, and where there is clinical suspicion, serological testing is crucial in diagnosis of *T. b. gambiense* disease. The sensitivity and specificity of currently available serological tests vary from 71% to 100% and 95% to 99%, respectively. In our patient, the high antibody titre supported a diagnosis of active trypanosomal infestation, although titres are known to remain high several years after treatment.<sup>6</sup>

MRI findings in trypanosomiasis are non-specific, ranging from meningeal enhancement in earlier CNS disease to bilateral confluent hyperintense T2 signals in the subcortical white matter in late disease, as seen in our patient.<sup>7</sup> Although not diagnostic, MRI is a useful adjunct in supporting the diagnosis as relatively few conditions cause this distinct MRI appearance, including acute disseminated encephalomyelitis, cerebral gliomatosis, the leukodystrophies and lymphoma, all of which were considered in our patient.

Non-specific CNS findings are meningoencephalitis, comprising leptomeningitis and encephalitis with diffuse perivascular white matter infiltration, microglial nodules and reactive astrocytosis.<sup>8</sup> The presence of Mott cells in the CNS and CSF is characteristic of HAT, but these cells are easily overlooked.<sup>9</sup> They are morula forms of plasma cells containing prominent eosinophilic cytoplasmic inclusions (Russell bodies) that stain positively with periodic acid-Schiff stain and are composed of immunoglobulin M. Although Mott cells can be found in myeloproliferative disorders, they are considered virtually pathognomonic of HAT in patients with appropriate clinical findings and exposure history.<sup>10</sup>

Early stage *T. b. gambiense* disease is treated with pentamidine. Eflornithine, an ornithine decarboxylase inhibitor that interferes with cell division, is the recommended first-line treatment for CNS disease.<sup>11</sup> Side effects include seizures, gastrointestinal upset and reversible myelosuppression. As it requires intravenous infusions four times daily over 2 weeks, it is not ideal in resource-constrained settings; recent studies suggest a combination of eflornithine and oral nifurtimox to be as effective but superior in ease of administration and duration of treatment (requiring eflornithine to be given only twice daily for 7 days).<sup>12</sup> From May 2009, the WHO has included combination therapy in its essential list of medicines for treatment of West African trypanosomiasis, but was unable to provide nifurtimox for our patient, as its use was approved at that time only for Chagas disease.

To our knowledge, our patient represents the fourth case of HAT identified in Australia. A case of meningoencephalitis thought to be due to *T. b. gambiense* was diagnosed in Perth in 2008 in an immigrant from Sudan and is also reported in this issue of the Journal<sup>13</sup> (page 417). A case due to *T. b. rhodesiense* was diagnosed at our institution in 1998 in a returned traveller with acute illness

**Lessons from practice**

- Human African trypanosomiasis (HAT) or sleeping sickness is rarely encountered in Australia; physicians should be aware of its possibility in individuals who present with meningoencephalitis and have lived in or visited endemic areas.
- Definitive diagnosis relies on parasite detection; in its absence, serological testing is the next most appropriate investigation, particularly for disease caused by *Trypanosoma brucei gambiense*.
- Corticosteroid therapy can mask symptoms of disease and falsely suggest an improvement, confounding the diagnosis.
- We recommend that individuals from endemic areas with clinically suspected HAT be screened serologically. This would prevent a potentially fatal delay in diagnosis and permit further monitoring and investigation to confirm and treat disease earlier. ♦

after visiting a Tanzanian game park.<sup>14</sup> The first case in Australia is said to have occurred after World War II.<sup>15</sup>

Our patient illustrates the need for clinicians to be aware of HAT as a potential cause of meningoencephalitis, particularly in African immigrants, for months or years after they move to Australia.<sup>16</sup> Had this possibility been recognised at presentation and specifically investigated, prompt treatment could have been given, and brain biopsy avoided.

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**Competing interests**

None identified.

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## LESSONS FROM PRACTICE

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