

Cryptococcal meningoencephalitis with fulminant intracranial hypertension: an unexpected cause of brain death

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ABSTRACT

The diagnosis of brain death requires the presence of unresponsiveness and a lack of reactivity, the absence of movement, breathing and brain stem reflexes, as well as a state of coma in which the cause has been identified. We report a case of brain death that was diagnosed based on clinical neurological examinations, and supported by the absence of cerebral blood flow on magnetic resonance angiography and electroencephalography demonstrating the characteristic absence of electrical activity. Thorough clinical examination and repeated imaging of the brain revealed no apparent clinical cause or mechanism of brain death. We proceeded with organ donation of the deceased's liver and corneas. However, postmortem revealed *Cryptococcus neoformans* meningoencephalitis as the cause of irreversible coma.

Keywords: brain death, cryptococcal meningoencephalitis, electroencephalography, intracranial hypertension, magnetic resonance angiography

Singapore Med J 2010;51(8):e133-e136

INTRODUCTION

The fungus *Cryptococcus neoformans* can cause common opportunistic infection in acquired immune deficiency syndrome (AIDS) patients. Cases also occur in patients with other forms of immunosuppression, such as transplants and cancers, and occasionally, in immunocompetent individuals. Meningoencephalitis is the most common manifestation of this disease. One of the most important neurological complications is the development of intracranial hypertension (ICH), which may result in high morbidity and mortality.^(1,2) We report the case of a 61-year-old patient who had undergone renal transplant and who was on immunosuppressants. The patient presented with nonspecific symptoms

and later developed fulminant cryptococcal meningoencephalitis, leading to brain death.

CASE REPORT

A 61-year-old Caucasian man presented with a two-week history of generalised malaise, loss of appetite, nausea, headache and unsteady gait with frequent falls. The patient was initially seen at a local hospital, where a non-contrast computed tomography (CT) of the brain did not reveal any abnormality. He was treated symptomatically with oral analgesics. The patient had end-stage renal failure secondary to hypertension and had undergone an autologous renal transplant from his wife one year ago. The patient was on prednisolone 10 mg once a day, tacrolimus 3 mg twice a day and mycophenolate (mofetil) 1 g twice a day for immunosuppression. He had persistent symptoms, as described above and was admitted to a tertiary hospital for further evaluation.

The patient was found to be afebrile and cardiovascularly stable, with a respiratory rate of 14 bpm and oxygen saturation of 98% on room air. Neurological examination revealed a Glasgow Coma Scale of 15 with full orientation to person, place and time. No meningism or focal neurological signs were observed. Laboratory results revealed normal haematology, biochemistry and liver function test, but the result for urea was 16.1 (baseline 10) mmol/L, creatinine 279 (baseline 200) mmol/L and lymphopaenia $0.41 \times 10^9/L$. Troponin and C-reactive protein levels were normal, and the serum tacrolimus level was not elevated. Electrocardiogram and chest radiograph were also normal.

The patient had a non-contrast CT of the brain, which did not reveal any intracranial bleeding, hydrocephalus or significant brain lesion. Clinically, he appeared dehydrated, and was treated with intravenous fluids. He was also given symptomatic treatment for his headache. The patient's subcutaneous erythropoietin therapy was ceased in view of it being a possible cause of his persistent headache. He was reviewed two days later by a neurologist, who suspected posterior reversible encephalopathy syndrome secondary to tacrolimus or a

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Fig. 1 Time-of-flight MR angiography image of the neck arteries shows a loss of signal in the internal carotid arteries from the level of bifurcation.

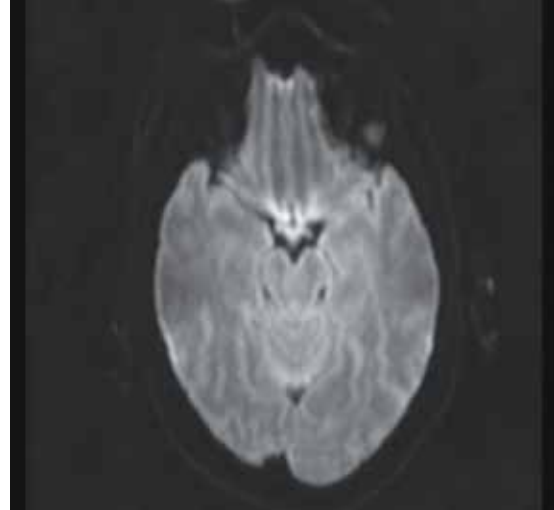


Fig. 2 Diffuse-weighted MR image of the brain shows diffuse restricted diffusion within the cerebral hemispheres.

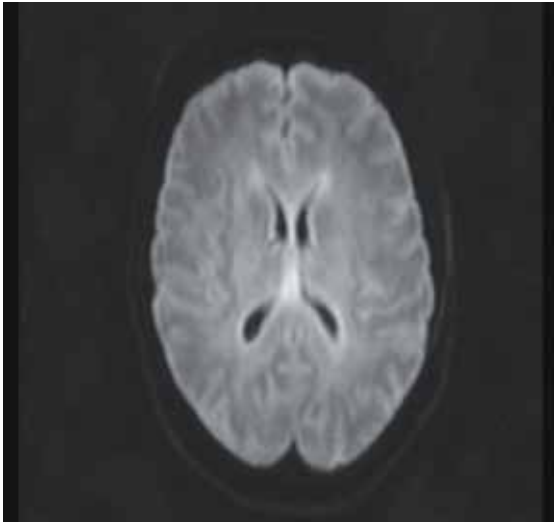


Fig. 3 Diffuse-weighted MR image of the brain shows diffuse restricted diffusion within the cerebellum.

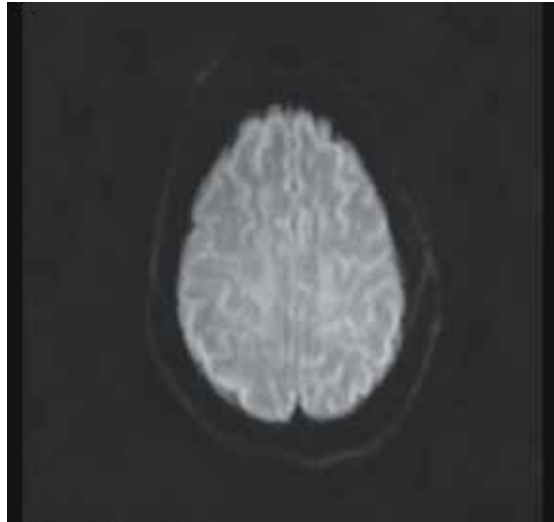


Fig. 4 Diffuse-weighted MR image of the brain shows diffuse restricted diffusion within the brainstem.

subacute brain infection. The patient was scheduled for magnetic resonance (MR) imaging and lumbar puncture over the next two days.

On the fifth day of admission, the patient was noted to be increasingly confused. He started to gasp and became suddenly unresponsive. The Medical Emergency Team was activated. The patient was found to be hypopnoeic, with a systolic blood pressure of 80 mmHg. He was immediately intubated, stabilised and transferred to the intensive care unit (ICU). At the time of collapse, the patient's pupils were dilated at 6 mm and non-reactive to light. Further assessment in the ICU revealed no spontaneous breathing or cough reflex to deep suctioning. A third CT of the brain (with contrast) on the same day showed no bleeding, space occupying

lesion, hydrocephalus or significant infarct. To exclude cerebral venous thrombosis, encephalitis or brainstem stroke that may not have shown up on CT of the brain, an MR imaging/angiography was performed. It showed partial effacement of the sulcal pattern and ventricles together with swelling of the cerebellum. In addition, the brainstem revealed patchy areas of high signal intensity. Poor flow signal was also noted in the anterior and posterior circulations, with evidence of diffuse restricted diffusion (Figs. 1–4). Electroencephalography (EEG) revealed complete loss of cerebral activity, even with intense somatosensory stimuli.

All the CT images and blood test results of the patients since admission were reviewed but did not show any abnormality that could explain the neurological

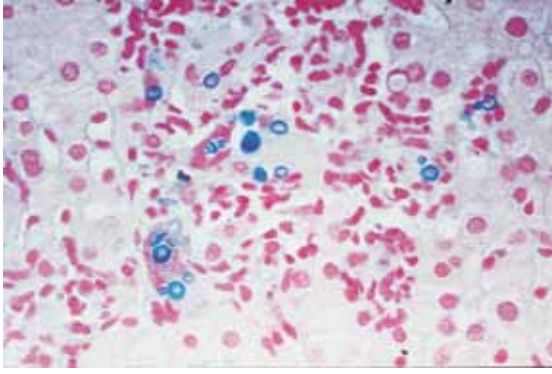


Fig. 5 Photomicrograph shows an alcian blue preparation of *Cryptococcus neoformans* surrounded by a characteristic wide gelatinous capsule in the brain tissue (Alcian blue stain, $\times 1,000$).

picture. The patient had not sustained any significant cardiorespiratory arrest that could cause hypoxic brain injury. We decided to proceed with clinical confirmation of brain death in light of the MR imaging/angiography findings. Upon clinical diagnosis of brain death, the patient was referred to the coroner for postmortem. At the same time, his family consented to organ donation, and both the liver and corneas were found to be suitable for donation. Postmortem biopsy of the brain tissue revealed cryptococcal meningoencephalitis (Fig. 5), and the patient's blood cryptococcal antigen (routine blood test of potential organ donor) was positive at $> 1 : 2,048$.

DISCUSSION

This case describes a renal transplant patient who presented with nonspecific symptoms for a duration of two weeks. In spite of the fact that repeated CT images of the brain were normal, the patient's neurological status deteriorated rapidly, which is consistent with brainstem herniation, resulting in brain death. We discuss the radiological findings in cryptococcal meningoencephalitis, its association with ICH and the implications of making a diagnosis of brain death without a known mechanism of injury.

The diagnosis of cryptococcal meningoencephalitis can be very difficult, given the subacute onset of symptoms and the nonspecific presentation. In most cases, clinical examination does not yield any meningism or positive neurological findings. CT images are frequently normal,⁽³⁾ or may reveal meningeal enhancement, single or multiple nodules (cryptococcomas), cerebral oedema or hydrocephalus. MR imaging is more sensitive for the detection of multiple enhancing nodules within the brain parenchyma, meninges, basal ganglia and midbrain. In this patient, two CT examinations performed over a period of five days did not aid in the diagnosis of the disease.

A high index of suspicion is warranted in AIDS patients and other immunocompromised individuals. Diagnosis can be made with Indian ink staining, culture or antigen tests on cerebrospinal fluid (CSF) obtained by lumbar puncture. Blood culture and serum antigen test are also helpful. Unfortunately, cryptococcal meningoencephalitis was not considered as a possible diagnosis initially, and the patient deteriorated rapidly to brain death without a lumbar puncture, blood culture or serum cryptococcal antigen assay.

Cryptococcal meningoencephalitis is often associated with intracranial pressure ≥ 200 mm H₂O in more than 50% of cases. In one study by Van der Horst et al, 13 out of 14 early deaths and 40% of deaths during Weeks 3–10 were associated with ICH.⁽²⁾ A CT or MR imaging of the brain commonly shows a normal ventricular size, and the mechanism is hypothesised to be the obstruction of CSF outflow by a large burden of yeasts and polysaccharide plugging the arachnoid villi.⁽³⁾ Our patient likely had severe ICH that was not evident on repeated CT imaging, which resulted in rapid brainstem herniation. Antinori et al reported two cases of cryptococcal meningoencephalitis that had brainstem herniation soon after lumbar puncture.⁽⁴⁾ A similar case has also been reported by Bromilow and Corcoran, where a patient with cryptococcal meningitis became brain dead within 90 minutes after lumbar puncture.⁽⁵⁾ However, Graybill et al suspected that inadequate CSF drainage and the resultant brain herniation, and not the lumbar puncture, was the cause of death in such cases.⁽¹⁾ In the case of our patient, it is unclear whether an early lumbar puncture would have been useful in making the diagnosis and reducing the ICH or hastened brainstem herniation and subsequent brain death. The current American guidelines recommend an opening pressure > 25 cm, daily serial lumbar punctures with withdrawals of large volumes of CSF to achieve a closing pressure ≤ 20 cm H₂O or 50% of the initial opening pressure.⁽⁶⁾

The declaration of brain death requires not only a series of careful neurological tests but also the establishment of the cause of coma, the ascertainment of irreversibility, the resolution of any misleading clinical neurologic signs, the recognition of possible confounding factors, the interpretation of the findings on neuroimaging and the performance of any confirmatory laboratory tests that are deemed necessary.^(7,8) In our patient, we did not intend to declare brain death without any cause or mechanism having been determined. However, instead of pinpointing the diagnosis, the MR imaging/angiography that was conducted to exclude encephalitis, brainstem lesions, venous thrombosis and other conditions demonstrated

evidence of brain death due to absent cerebral blood flow. The EEG investigation also supported the diagnosis of brain death instead of diagnosing encephalopathy. We used the unequivocal MR angiography and EEG findings to support the diagnosis of irreversible, catastrophic damage to the brain, much as a CT imaging indicating massive intracranial haemorrhage would be used in this setting. At that point, we were still unaware of the cause of this irreversible, catastrophic damage. We then proceeded to conduct clinical tests that confirmed brain death in the usual way. Although it was not an optimal clinical situation, we declared our patient brain dead without a known cause. It was only after the postmortem that the diagnosis of cryptococcal meningoencephalitis was determined as the mechanism of brain death.

This case illustrates that it is not always possible to determine the underlying cause or mechanism before declaring brain death. But this should not deter us from referring appropriate patients for organ donation as long as all the essential investigations to find the cause have been conducted. The initial step in the diagnosis of brain death, i.e. clear evidence of irreversible brain damage, was supported by the unequivocal MR imaging/angiography and EEG findings. We then proceeded with clinical brain death testing as per the protocol.

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