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Commentary Open Access

Cryptococcal Meningitis with Cerebral Herniation

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Commentary

Cryptococcus neoformans (*C. neoformans var. grubii* and *C. neoformans var. neoformans*) and *C. gattii* are responsible for most cases of cryptococcal meningitis worldwide [1]. The disease of cryptococcal meningitis has been well documented in patients with acquired immune deficiency syndrome (AIDS) and it may also occur in human immunodeficiency virus (HIV)-negative patients even with apparently normal immune systems [2,3]. The median age of 38.5 years at presentation in the non-HIV patients is similar to that in the HIV population (median age, 36 years) [2,4]. Chinese population seems to be more vulnerable than other ethnic groups to cryptococcal meningitis in the previously healthy patients [5]. However, the diagnosis is easily delayed and the disease manifestations may be more severe in cryptococcal meningitis of the immunocompetent patients than in immunocompromised patients [4]. The most common underlying condition in Chinese patients with cryptococcal meningitis is corticosteroid use [4], which has sometime been added illegally to traditional herb drug medication.

Moreover, it has been shown that mutative genotype coding for mannose-binding lectin (MBL) deficiency is associated with cryptococcal meningitis in HIV-uninfected Chinese patients, particularly in immunocompetent patients [6]. As the levels of MBL fluctuate with MBL gene polymorphism in systemic lupus erythematosus (SLE) patients [7] and a general hypomethylated state of T and B lymphocyte genes has been observed in SLE patients with inhibited DNA methyl transferases (DNMTs) efficacy [8,9], aberrant DNA methylation patterns might directly lead to the abnormal expression of MBL and perhaps cause cryptococcal meningitis in humans. Therefore, study the stability of enzymes that required for the establishment and maintenance of DNA methylation, including DNMTs and some histone methyltransferases [10-12], might be a new direction for the early recognition of patients who are at risk for cryptococcal meningitis.

Morbidities of cryptococcal meningitis are high, with seizures, cranial nerves palsies, obstructive hydrocephalus, increased intracranial pressure (IICP), cerebral edema and herniation (Figure 1). In a retrospective review of 154 non-HIV-infected patients with cryptococcal meningitis in China, the morbidities included seizures (28.6%), cranial nerves palsies (51.5%) and cerebral herniation (19.5%), with attributable and one-year overall mortality rates of 19.6% and 28.7%, respectively [4]. Patients with delayed diagnosis of cryptococcal meningitis experience more brain herniation, coma, seizures, hydrocephalus and more surgical shunt procedures [4]. Delay in the diagnosis of hydrocephalus may be accompanied with IICP and could thereby cause a deterioration of consciousness [13].

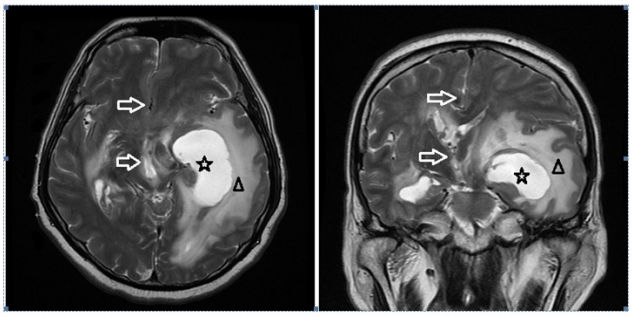

Figure 1: MRI showing dilated third ventricle (star) and periventricular white matter edema (arrow head), causing midline shifting (arrow), transtentorial and subfalcine herniation, in a previously healthy middle-aged patient with a cryptococcal antigen titer of 1:1024 in the CSF.

Clinical manifestations may include nausea, vomiting, severe frontal headaches, neck stiffness, dizziness, impaired balance, oscillopsia, blindness, paraparesis, unsteadiness of gait and somnolence [14]. Radiographic image of the brain with computed tomography (CT) or magnetic resonance image (MRI) plays an important role in detection of the central nervous system (CNS) morbidities. Brain CT may show normal appearance, severe cerebral edema, hydrocephalus or tonsillar herniation. Besides, MRI is superior to CT in detecting CNS abnormalities, such as leptomeningeal enhancement and ventriculitis, in patients with cryptococcal meningitis [15]. In a recent retrospective review of immunocompetent patients with cryptococcal meningitis, multiple intraparenchymal lesions were more common than leptomeningeal enhancement in the brain MRI radiographs [16]. The cryotococcal fungi could be isolated in the cerebrospinal fluid (CSF), leptomeninges and parenchyma of the brain [17]. Cryptococcus antigen titer is usually positive in the CSF and/or serum. Nevertheless, it could happen that Cryptococcus antigen is positive in the serum but negative in the CSF [18].

Treatment of cryptococcal meningitis remains a challenge. Three most important managements have been highlighted: (1) induction therapy for meningococcal encephalitis with antifungal agents followed by suppressive regimens using fluconazole; (2) the use of lipid formulations of amphotericin B regimens in patients with renal impairment; and (3) early recognition and management of IICP [19,20]. Prompt relief of hydrocephalus is useful for the patients who show rapid deterioration of consciousness or signs of cerebral herniation. Lumbar puncture may have to be initiated or repeated sooner in managing IICP or if physicians have a concern about

potential microbiologic failure [19]. Permanent ventriculoperitoneal (VP) shunt placement is a safe and effective way of therapy [13,21-24], even in the status of IICP (>500 mm CSF) without evidence of hydrocephalus [20]. Besides, premedication with antifungal drugs before surgical procedure is unnecessary [24].

Delay in the diagnosis or treatment of patients with hydrocephalus is associated with poor outcome [4]. Control of intracranial pressure could be one of the most important determinants of outcome [21-24]. Patients with hydrocephalus whose Glasgow coma scale >9 had been shown to have better outcome following permanent shunt placement [21]. However, the duration of disturbance of consciousness or change of mentality before shunting is critical in determination of the outcome of the treatment [24].

In conclusion, cryptococcal meningitis with hydrocephalus and cerebral herniation may be refractory to antifungal therapy and VP shunting. As sequential changes of brain abnormalities may occur any time throughout the disease course, further imaging study is important in followed up of patients with poor consciousness and responsiveness to treatment although treatment is undergoing and several image studies have already been performed.

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