HUMAN IMMUNODEFICIENCY VIRUS (HIV) RELATED CRYPTOCOCCAL MENINGITIS IN RURAL CENTRAL THAILAND – TREATMENT DIFFICULTIES AND PREVENTION STRATEGIES

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Abstract. In 2000, cryptococcal meningitis was a common HIV related opportunistic infection in central Thailand requiring inpatient management but few patients suffering from it could afford a full course of treatment once infection had occurred. Since then, the production of generic fluconazole and highly active antiretroviral therapy (HAART) in Thailand (and national guidelines regarding their use) is reducing the incidence of this condition and such a strategy of prevention appears much more effective than treating established disease. There remains a continuing need for health education in the region and the removal of stigma associated with this disease so that earlier detection of HIV infection and the implementation of these national guidelines can have their greatest impact.

INTRODUCTION

Fungal infections complicate infection with untreated HIV, ranging from asymptomatic mucocutaneous candidiasis to life-threatening systemic mycoses including cryptococcal meningitis.

Cryptococcal meningitis is the third most common HIV related opportunistic infection in Thailand, occurring in nearly 20% of acquired immunodeficiency syndrome (AIDS) patients nationwide (Chariyalertsak *et al*, 2001). In central Thailand it was found to be the commonest HIV-related reason for hospital admission and the commonest AIDS-defining illness in patients presenting for the first time for review at a specialist AIDS clinic (Inverarity *et al*, 2002). Extrapulmonary cryptococcal infection shows considerable regional variation in Thailand, affecting 24.1% of AIDS patients in the northeast and only 6.9% in the south (Chariyalertsak *et al*, 2001). While the availability of intravenous amphotericin B in developed countries has reduced the mortality rate from cryptococcal meningitis, it remains high in developing countries and survival is often short after the diagnosis of cryptococcal meningitis is made. For instance, studies in Zimbabwe and Uganda respectively showed the median survival following diagnosis to be 14 and 26 days (Heyderman *et al*, 1998; French *et al*, 2002; Nelson and John, 2004).

Manorom Christian Hospital (MCH) is a 49-bed mission hospital in the province of Chainat in central Thailand which is located on the flood plain of the Chao Phraya River Valley. The region is agricultural and the economy dependant on rice farming. Most patients are of low socioeconomic class with low paying jobs - mainly farming or hired labor. As a result, many cannot afford fourteen days of amphotericin B for the optimal initial treatment of cryptococcal meningitis. At the time of this study, primary prophylaxis with antifungal therapy had not been recommended for HIV infected patients and highly active anti-retroviral therapy (HAART) was not

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widely available.

In addition, at this time in the rural Thai population there was a tendency to present only at an advanced stage of HIV infection. A combination of factors contributed to this behavior including denial, a fatalistic belief that nothing could be done, fear of being deserted by relatives and a fear of confidentiality being breached and their diagnosis becoming more widely known. Hospital admission for treatment was often not favored by patients or their relatives. The reasons for this were often the cost of treatment, fear that confidentiality would be broken, religious and cultural factors leading to a preference to die at home, no available relative to care for the patient during admission and failure to respond quickly to treatment.

We reviewed the management of AIDS related cryptococcal meningitis at MCH to illustrate some of the problems faced in managing this condition in the region.

PATIENTS AND METHODS

A retrospective case series of the 32 adult HIV-infected patients admitted to MCH between 1st January 1999 and 30th June 2000 for the treatment of proven cryptococcal meningitis was compiled.

Cryptococcal meningitis was diagnosed using both an India Ink preparation and a cryptococcal antigen latex agglutination test (Mahidol University, Bangkok) on cerebrospinal fluid (CSF) from patients whose symptoms were consistent with the diagnosis.

Patient's demographic details, duration of admission, number of readmission episodes and cases with fatal outcomes in the hospital were recorded. This information was obtained from ward admission books, medical case notes and hospital finance department records.

RESULTS

There were 49 admission episodes for 32 patients (including 7 patients admitted twice, 2 patients admitted four times and 1 patient admitted 5 times). Of these, only 7 patients (22%) were female. There were only 2 inpatient deaths and both were women. The mean age of males was 33 years (standard deviation = 6 years) and for females it was 32 years (standard deviation = 10 years). The duration of admission ranged from 1 to 28 days (median = 4 days) but only 3 patients remained in hospital for over 14 days. The mean daily cost of admission and treatment was 1907 baht (standard deviation = 1,043 baht), although the minimum daily wage in this region of Thailand in 2000 was between 130 to 163 baht.

DISCUSSION

This study highlights several difficulties that were experienced in caring for Thai patients infected with HIV-related cryptococcal meningitis. Thankfully, some of these difficulties which were faced throughout Thailand have been addressed by the Thai Ministry of Public Health in subsequent years.

As systemic and local fungal opportunistic infections among Thai patients infected with HIV were so common, it was believed primary antifungal prophylaxis could improve survival (Nightingale *et al*, 1992; Powderly *et al*, 1995; Singh *et al*, 1996; Havlir *et al*, 1998; McKinsey *et al*, 1999; Chariyalertsak *et al*, 2002). This was corroborated in a study by Chetchotisakd *et al* (2004) which suggested that weekly fluconazole prophylaxis reduced the overall mortality from fungal opportunistic infections such as cryptococcal meningitis. Since 2002, the Thai Ministry of Public Health national guidelines for the clinical management of HIV infection in children and adults have recommended a weekly 400 mg dose of fluconazole for patients with a CD4 count < 100 cells/mm^3 (Department of Disease Control, 2002). Local production of fluconazole in Thailand has dramatically reduced its price and improved access to this effective antifungal drug. Even so, for those who are known to be severely im-

munosuppressed and for whom primary antifungal prophylaxis has been recommended, the uptake remains low. In northern Thailand, only 39% of hospitals surveyed and 3% of community health centers reported providing primary prophylaxis for the prevention of cryptococcal meningitis (Leusaree *et al*, 2004; Thanprasertsuk *et al*, 2006). Possible reasons may be the limited availability of drugs and inadequate training of health care personnel.

The Government Pharmaceutical Organization (GPO) of Thailand produces a number of generic antiretroviral drugs including zidovudine, didanosine, lamivudine, stavudine, nevirapine and nelfinavir. This has dramatically lowered the cost of these medications to about 1,200 baht (US$ 30) per month (Thanprasertsuk *et al*, 2006). The National Access to Care Program provided HAART to a limited number of patients at selected hospitals between 2000 and 2002. In November 2003 the Ministry of Public Health launched an expanded program to provide a limited number of HAART regimens free to 50,000 AIDS patients nationwide (Thanprasertsuk *et al*, 2006). Patients seen at MCH have been included in this initiative. As a result of these two initiatives, the incidence of cases of cryptococcal meningitis is decreasing in the region.

However, for those with cryptococcal infection in this resource-poor population, the initial fourteen day treatment course with amphotericin B is still beyond the resources of most patients. Shortened courses of treatment in our patient population were associated with a high rate of relapse and readmission.

Cryptococcal meningitis was often a presenting opportunistic infection for patients with undiagnosed HIV infection. In such cases the window of opportunity for primary prophylaxis had been missed. There is a need for continued community-based education efforts, voluntary counselling and testing facilities, and improved access to antifungal prophylaxis and HAART. Preventative strategies are even more important given the findings of Pitisuttithum *et al* (2001) who found that high-dose amphotericin B was not as effective as previously thought in the treatment of cryptococcal meningitis in a Thai population. Efforts by the Thai Ministry of Public Health to maintain and improve the health infrastructure in this region and provide these services are welcomed.

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