

## Cryptococcal meningitis in patients with non-HIV and HIV infection: a clinical study

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### Abstract

The medical records of patients with cryptococcal meningitis (CM) at Ramathibodi hospital during the periods 1993-1994 and 1977-1988 were retrospectively reviewed. When comparing the period 1993-1994 to the earlier period, there was a 10-fold increase in the annual hospital admission of CM which occurred exclusively in patients with HIV infection. In the period 1977-1988, which was before the onset of the AIDS epidemic in Thailand, 37% of the patients had associated diseases. Although the patients in both groups presented with similar symptoms, the duration of illness before diagnosis was shorter in patients with HIV. The CSF of the HIV patients had less pleocytosis; 28% had normal number of white blood cell. In spite of this, there was higher positivity in India ink smear (88%) and culture (100%), suggesting a heavier infection with less cellular immune response. The CSF of the patients in the period 1977-1988 had higher pressure, more pleocytosis and higher protein content despite lower positivity in India ink smear (68%) and culture (80%), indicating greater inflammatory response, lower fungal load and more frequent CSF flow blockage.

Patients without HIV infection received a mean total dose of 2.3 gm amphotericin B and 150 mg/kg/day of flucytosine. Ventricular shunt was performed in those with intracranial hypertension refractory to conservative treatment. The mortality was 6%. The patients with HIV was treated with variable dosages of amphotericin B, followed by oral fluconazole or itraconazole and long term antifungal prophylaxis. Intracranial hypertension was treated with repeated lumbar punctures and continuous spinal subarachnoid drainage. The immediate mortality was much higher at 60% and 30% of the patients was still alive at the end of 1 year.

*Key Words:* Cryptococcosis, Thailand, HIV

### INTRODUCTION

The epidemic of HIV infection has resulted in great changes in the epidemiology of various infectious diseases, particularly those of the nervous system.<sup>1</sup> In Thailand, before the epidemic of HIV infection, cryptococcal meningitis (CM) was uncommon and was sporadically seen throughout the years. Since the epidemic of AIDS there has been a marked increase in the incidence of CM which occurred mainly in patients with HIV infection.<sup>2</sup> Currently it has become the most common cause of meningitis in Thailand. This is a comparative clinical and laboratory study of CM admitted to the Department of Medicine, Ramathibodi Hospital in two periods, 1977-1988 and 1993-1994. The former is before the epidemic of AIDS in Thailand. Ramathibodi Hospital is a

university hospital in Bangkok.

### MATERIALS AND METHODS

Medical records of patients diagnosed as having CM with or without concomitant diseases in two periods: 1977-1988, and 1993-1994 were reviewed. The diagnosis of CM was based on the detection of the *Cryptococcus neoformans* organism in the CSF by India ink preparation, culture or detection of the antigen by latex agglutination. As there was no report of HIV infection in Thailand during the first period, these patients represented cases of CM without HIV infection.

The data analysed included clinical profiles and CSF parameters obtained by the first lumbar puncture. Cryptococcal antigen was detected by latex agglutination test developed in our hospital.<sup>3</sup>

The presence of antibody to HIV was confirmed by the gel-particle and ELISA technique.

## RESULTS

During the first study period (1977-1988), 32 patients with CM were seen. Associated diseases were found in 12 patients (37%). The details of the associated diseases is shown in Table 1. During the second study period (1993-1994), 67 CM patients were seen. The meningitis occurred exclusively in patients with HIV infection. Figure 1 shows the number of the admissions for CM in each year under study. Thus, from the first study period to the second, the annual admissions for CM increased by about tenfolds, from 3.2 per year (1977-1988) to 33.5 per year (1993-1994). The patient profile of the two study groups is listed in Table 2. As shown, the mean age of the patients was similar, but the male to female sex ratio is much higher in the HIV infected group (6.4:1 versus 1.5:1).

Figure 2 shows the duration of illness before diagnosis. Table 3 lists the presenting symptoms and signs. The duration of illness before diagnosis is shorter in patients with HIV infection. About one third of patients with HIV had duration of illness of <1 week. On the other hand, more than a quarter of the non-HIV patients, and none of the HIV patients had duration of illness of >12 weeks. Headache was a universal symptom for both groups. Fever, neck stiffness and papilloedema were also frequently seen. Headache with fever and neck stiffness were significantly more common among the patients with HIV infection.

The changes in CSF is shown in Table 4. As shown, high CSF opening pressure, pleocytosis, low sugar and high protein were common to both groups of patients. However, very high opening CSF pressure of >400mm H<sub>2</sub>O,

**TABLE 1: Associated conditions in non-HIV patients with cryptococcal meningitis**

Associated diseases	Number of patients (total no: 32)
SLE on prednisolone	7
HbE disease	2
Chronic active hepatitis	2
Diabetes mellitus	1
Disseminated herpes zoster	1
Disseminated tuberculosis	1

**TABLE 2: Patients profile in non-HIV and HIV associated cryptococcal meningitis**

	non-HIV	HIV
Number of cases	32	67
Male	13	58
Female	19	9
Male : Female	1.5:1	6.4:1
Age	12-57	20-56
Mean age	35.6	32.6

pleocytosis with white blood cells >100/mm<sup>3</sup> were more common in the non-HIV patients. The only patient with markedly high protein of >500mg% was also not infected with HIV. On the other hand, 28% of the HIV patients had cell count of <5 lymphocytes/mm<sup>3</sup>, which is within normal limits. Figure 3 lists the positivity rate of the cryptococcal detection in the CSF by three different methods. As shown, despite the relative lack of cellular response in the CSF, positive smear by India ink preparation was seen in 88%, and positive culture in 100% of the HIV patients. The corresponding figures for the non-HIV patients were lower at 68% and 80% respectively.

All the non-HIV patients received intravenous amphotericin B with average total dose of 2,289 mg (range 100 to 3,465 mg). 94% of the cases also received flucytosine at 150 mg/kg/day. The regimen required an average hospital stay of 76 days. Ventriculo-peritoneal or theco-peritoneal

**TABLE 3: Symptoms and signs at time of presentation**

	non-HIV %	HIV %
<b>Symptoms</b>		
Headache and fever *	53	78
Headache only *	41	20
Change of consciousness *	36	15
Convulsion	15	11
Diplopia	12	17
<b>Signs</b>		
Neck stiffness *	53	83
Papilledema	41	33
Cranial nerve palsies	12	17
Weakness	6	2

\* p < 0.05

**TABLE 4: CSF parameters in the first lumbar puncture**

	non-HIV %	HIV %
Open CSF pressure (mmH <sub>2</sub> O)		
< 200	23	41
200 -399	41	44
> 400 *	36	15
Cells in CSF ( cell/mm <sup>3</sup> )		
< 20 *	17	44
20-99	23	42
100-499 *	47	14
> 500 *	11	0
CSF/Blood glucose (%CSF/blood)		
< 50	79	82
> 50	21	18
CSF protein (mg%)		
< 40	9	26
40-499	88	75
> 500	4	0

\* p < 0.05

shunts were placed in patients who had severely increased intracranial pressure refractory to conservative treatment. There were 2 mortalities (6%). Both had very high opening CSF pressure of >600 mm H<sub>2</sub>O.

There was no uniform antifungal policy for HIV-related CM during the period of study. Most patients received variable doses of

intravenous amphotericin B, followed by high oral doses of fluconazole or itraconazole for 10-12 weeks. For the patients who could be followed-up regularly, maintenance oral fluconazole or itraconazole were given to prevent relapses. Raised intracranial pressure was treated by repeated lumbar puncture or continuous spinal subarachnoid drainage in a closed system.

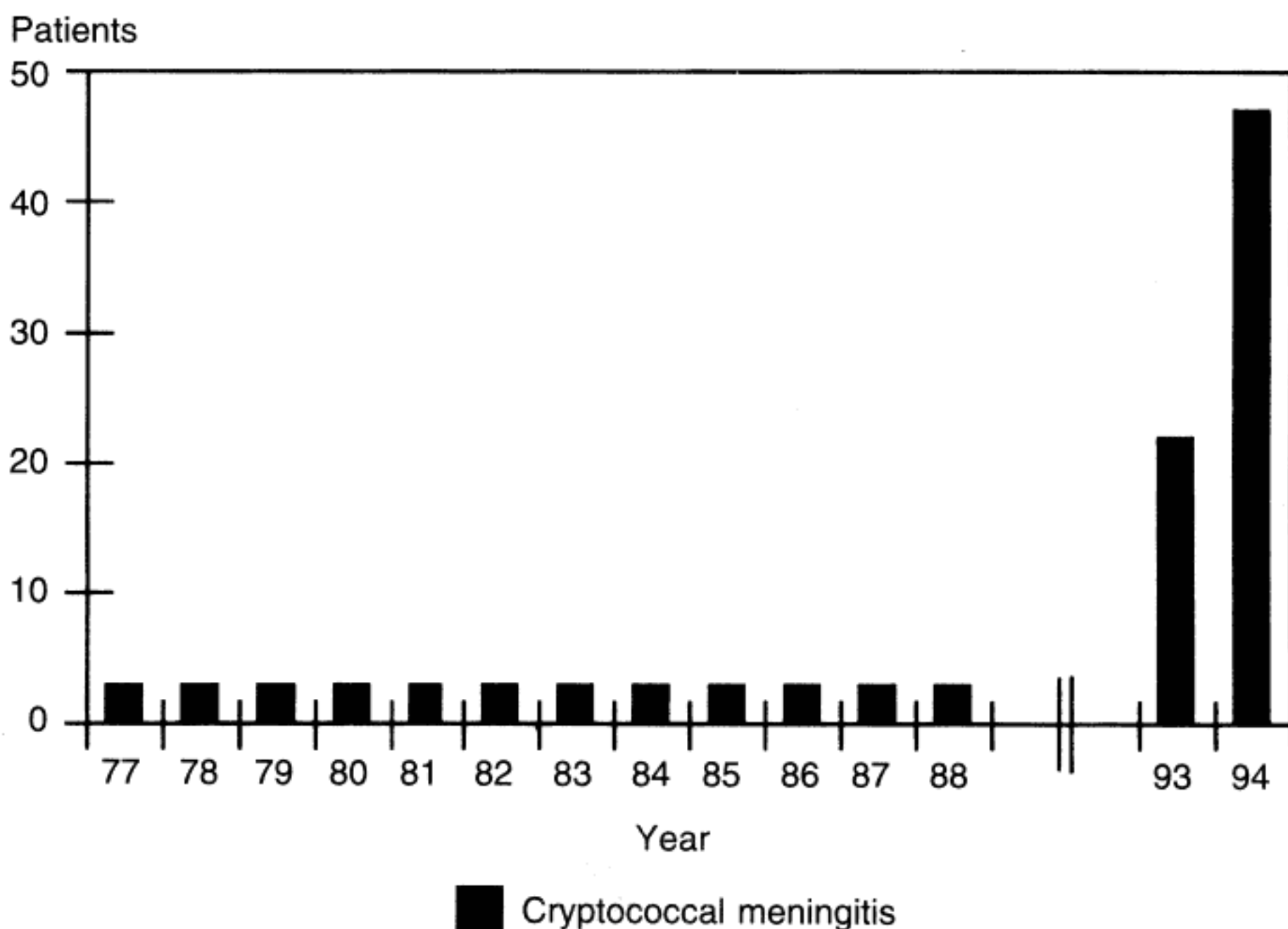


FIG 1: Number of patients with cryptococcal meningitis admitted to Ramathibodi Hospital.



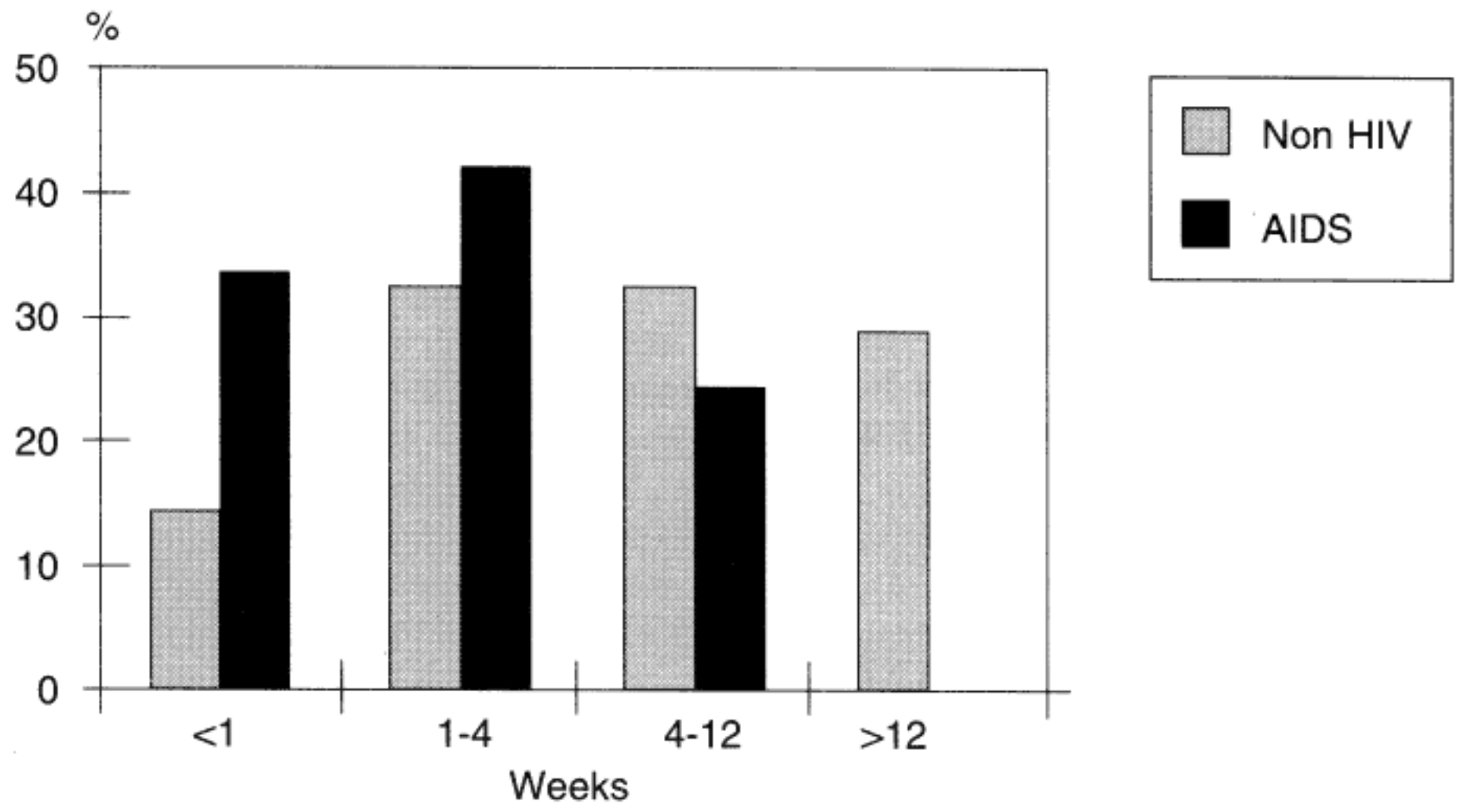


FIG 2: Duration of illness before the diagnosis was made.

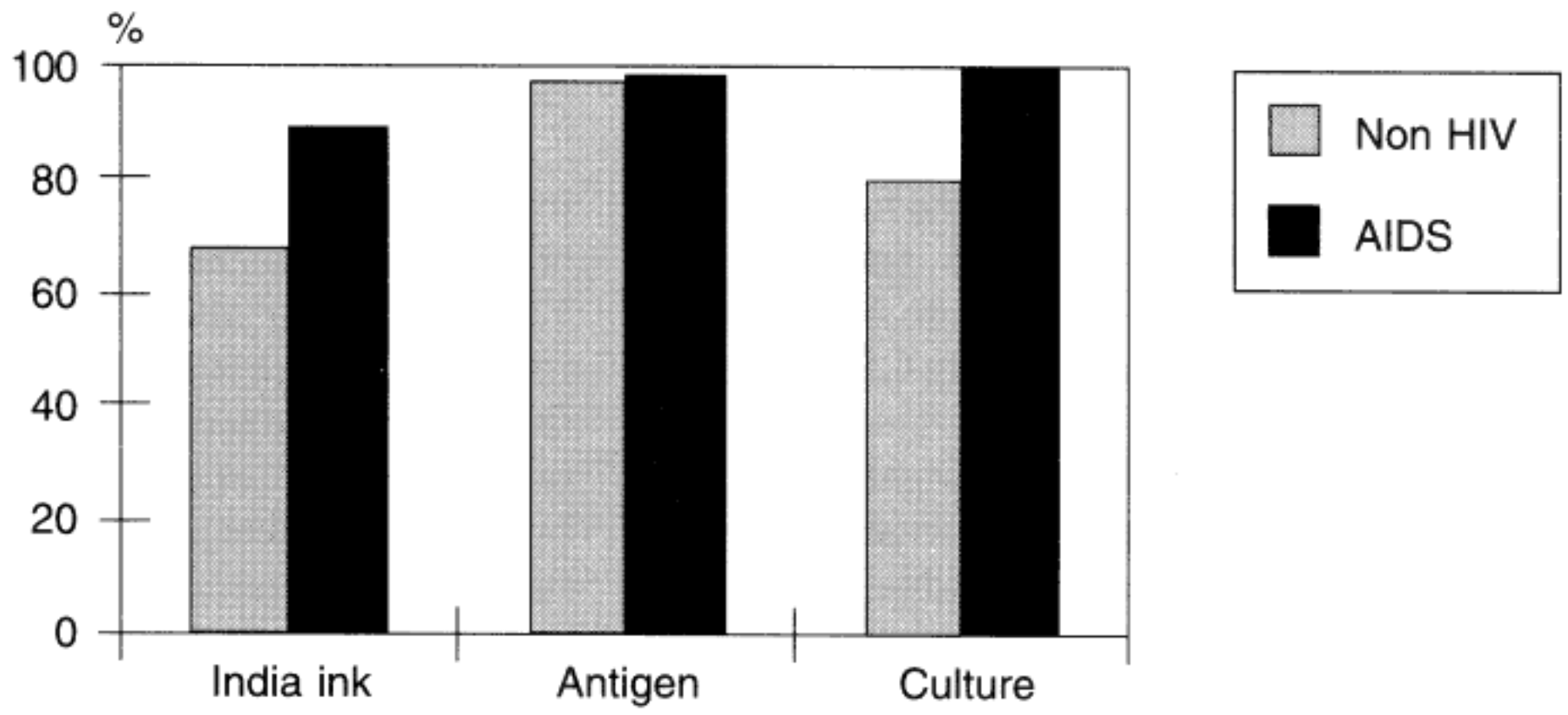


FIG 3: Methods of detection of cryptococcus neoformans in CSF.

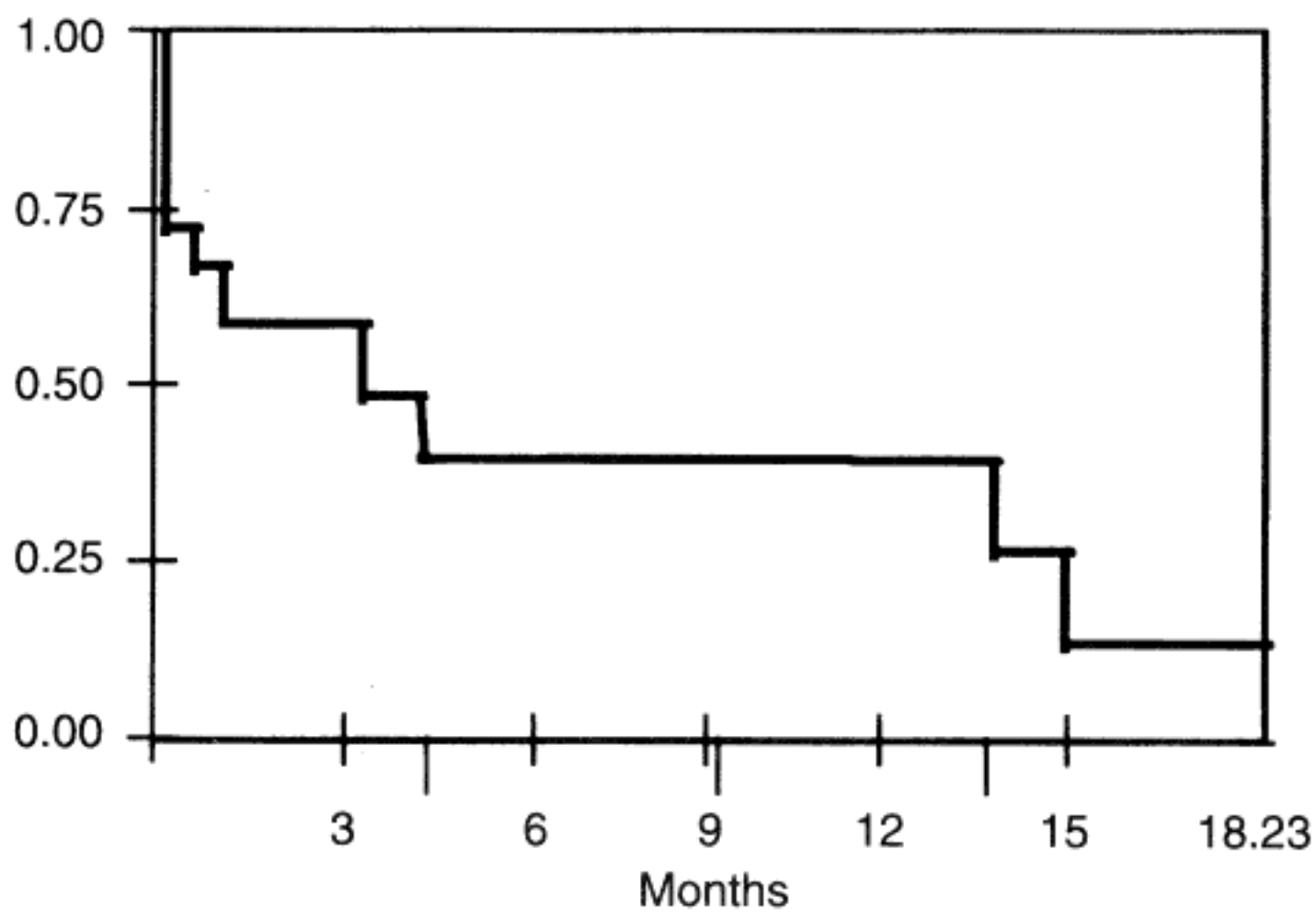


FIG 4: Kaplan-Meier survival curve of HIV-seropositive patients with cryptococcal meningitis in Ramathibodi Hospital.

The difference in the outcomes of CM in the non-HIV and HIV groups was striking. The mortality was 6% for the non-HIV group and 60% for the HIV group. The Kaplan-Meier survival curve of the HIV patients is shown in Figure 4. About 30 % of the patients remained alive at the end of one year.

## DISCUSSION

Information on the epidemiology of cryptococcal meningitis in Thailand is incomplete.<sup>4</sup> Ramathibodi Hospital is a general hospital in Bangkok. The data presented in this study is probably similar to other general hospitals in the various parts of the country. The incidence of CM hospital admissions in the period 1977-1988 was also equivalent to those reported from similar hospitals in Malaysia and Singapore.<sup>5,6</sup> The ten-fold increase in the incidence of CM in the period 1993-1994 clearly demonstrates the impact of HIV. The hospital admission of CM in Ramathibodi Hospital, a major referral teaching hospital in the capital city do not however reflect the magnitude of the HIV problem in the country.<sup>7</sup> Many hospitals in the periphery have now acquired the skills in managing CM in HIV patients, and do not refer the patients.

The shorter duration of symptoms before diagnosis in the group with HIV can be explained by a rapid progression of illness or greater awareness of complications of meningitis among the HIV-seropositive patients. Headache with or without fever in patients with HIV should alert physicians to the possibility of CM. A larger proportion of our patients had neck stiffness (83%), compared to other series reported in the literature, the corresponding figure in the literature being one-quarter to one-third of the patients.<sup>8,9</sup> This may be due to the later stages of the disease in our patients at the time of diagnosis.

Elevation of intracranial pressure, a major complication of CM which is associated with increased risk of early death<sup>10,11</sup> was found in more than 60% in both our patient groups. The very high opening pressure of >400 mm H<sub>2</sub>O was significantly more frequent in the non-HIV patients. Papilloedema was also common, seen in 41% non-HIV and 33% HIV infected patients. There was less pleocytosis in CSF from patients with HIV. This finding is similar to previous studies.<sup>12</sup> 28% of the HIV group in our series had normal white cell counts in the CSF. Thus, if the first sample is normal, repeated CSF should be done in HIV patients suspected to

have meningitis. Positive smear by India ink preparation was positive in 88% of the HIV group of patients. This simple test can be done in a primary care setting. In view of the high prevalence of CM in HIV, India ink smear should be routinely done in every CSF examination. Latex agglutination test for cryptococcal antigen and culture are the other specific and sensitive tests for the diagnosis of CM. The relative absence of CSF pleocytosis in HIV patients is most likely a reflection of the lack of immune cellular response from the underlying immunological deficiency. The higher positivity of India Ink smear and culture in these patient indicates that due to this relative poverty of immune cellular response, there was heavier infection from a larger number of offending organisms. On the other hand, the greater inflammatory response with higher CSF pleocytosis and protein in the non-HIV patients may cause CSF flow blockage over the surface of the cerebral hemispheres and arachnoid granulations resulting in the higher CSF pressures noted above.

The mainstay of CM treatment is antifungal chemotherapy. In a small study, the classical combination therapy of amphotericin B and flucytosine has superior mycological and clinical efficacy when compared to fluconazole alone in HIV patients.<sup>13</sup> Larsen et al reported that fluconazole when combined with flucytosine, was able to increase the rate of success. However about a quarter of the patients had severe side effects leading to withdrawal of flucytosine.<sup>14</sup> Fluconazole has been shown to be as efficacious as amphotericin alone and may be adequate for low risk patients with mild disease.<sup>9</sup> Fluconazole is superior to weekly intravenous amphotericin B as long term prophylaxis to prevent relapses after primary treatment in HIV patients.<sup>15</sup> Most of our HIV patients were treated with intravenous amphotericin initially, followed by oral fluconazole or itraconazole.

Intracranial hypertension, a common and important complication which is often overlooked, is associated with increased mortality<sup>10,11</sup> and morbidity.<sup>5</sup> Relief of high CSF pressure by repeated lumbar punctures, continuous external drainage or shunting procedures should be done apart from the antifungal treatment. This is in spite of normal ventricular size on the CT scan.<sup>5</sup>

It remains a great problem to manage large numbers of HIV patients with CM, when the long term outcome of the patient is poor, and the results of antifungal chemotherapy often

incomplete and slow, especially in a community with restricted resources.

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