THE CLINICAL AND LABORATORY SETTING OF *CRYPTOCOCCAL* MENINGITIS AS SEEN AT UNIVERSITY TEACHING HOSPITAL, LUSAKA AND TO EVALUATE EFFICACY OF FLUCONAZOLE IN ITS THERAPY

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APPROVAL PAGE

THIS DISSERTATION OF Dr. MWABA PETER IS APPROVED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE MASTER DEGREE IN INTERNAL MEDICINE.

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THE CLINICAL AND LABORATORY SETTING OF ***CRYPTOCOCCAL*** MENINGITIS AS SEEN AT UNIVERSITY TEACHING HOSPITAL (UTH), LUSAKA AND THE EFFICACY OF FLUCONAZOLE IN IT'S THERAPY.

CONTENTS

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ABSTRACT

Three hundred and sixty seven patients with ***cryptococcal*** meningitis were seen during the period from December, 1995 to December, 1996 though only one hundred and thirty patients were actually recruited.This was a prospective study designed to determine the prevalence of ***cryptococcal*** meningitis at the University Teaching Hospital and to determine its clinical setting, laboratory setting and the efficacy of Fluconazole as prime therapy in its treatment as is the practice in the hospital at the moment.

Cryptococcal meningitis is now the leading cause of meningitis in the University Teaching Hospital and affects predominantly patients who are under forty five years old (82.5%) though its sex ratio seems to be 1:1. It primarily occurs in the setting of immunosuppression as the HIV seropositivity was 96.15% in patients evaluated and the CD_4 counts were below 200 in 83.33% of the patients.

The study has confirmed that ***cryptococcal*** meningitis is a cause of chronic meningitiswith a mean duratiion of presentation of twenty one days before diagnosis is made. And with 96.15% of the cases being seropositive for HIV infection, it is clearly an AIDS defining finding.

Other features are non-specific and are mainly those of chronic ill health, pruritic rash, oral candidiasis and recurrent enteritis. Papilloedema occurs in 18.5% of patients while none of the patients had visual loss. Neck rigidity and other signs of meningitis may or may not be present.

Cryptococcal meningitis is associated with a high mortality. Even though patients were exposed to six weeks of Fluconazole at the accepted dosage 84.09% had died within this period. With better results known to occur with other regimen such as Amphotericin B and Flucytosine, it may be concluded that Fluconazole is not a drug of first choice. For the moment, it is suggested that UTH reverts to standard therapy as is the practice elsewhere.

1.1 MICROBIOLOGY OF *CRYPTOCOCCUS*

This fungus was first isolated in 1864 from fruit juice by Sanfelice. Older names of this fungus include ***European blastomycosis*** and ***Torula histolytica***. Other ***cryptococci*** have not been shown to cause disease in man so far.

The fungus lives freely in soil enriched by pigeons dropping. It is a dimorphic fungus which has a large poly saccharide capsule on which five serotype designated A,B,C,D, or AD are found. The cell is round or oval usually 4-6μm in diameter and reproduces by budding.

a. Identification

On solid culture media, ***cryptococcal*** colonies are smooth, convex and yellow or tan. It usually, unlike other species of ***cryptococci***, grows at 37°C, does not produce pseudomycelia on cornmeal or twan agar and hydrolyses urea. ***Cryptococcus*** does not ferment glucose and mouse pathogenicity is quite specific to it unlike other species. ***Cryptococcus*** also has the unique property of melanin production.

b. Serotype

Cryptococcus has mainly four different serotypes; A,B,C,D though some strains react to A and D. Serotyping is usually performed using agglutination or immunofluorescence procedures. Serotype A and D can be mated to produce the sexual form ***Filobasidella neoformans var neoformans*** and believed to be responsible for the disease in Southern

Africa while B and C are classified as ***C. neoformans var gattii*** and tend to be more common to Papa New Guinea where they cause disease.

c. Ecology and Epidemiology

Cryptococcus is a saprobe in nature with a worldwide distribution rather than any defined endemic area. Usually, the habitat is aged pigeon droppings as well as nesting places such as window ledges and barns. Though pigeon droppings are a natural habitat, the pigeons do not get infected.

Much less commonly, ***C. neoformans*** has been isolated from juice and a variety of other sources in nature. Naturally acquired ***cryptococcosis*** occurs in animals as well as humans but animal to person transmission has not been documented and has been proved by non occurrence of ***cryptococcosis*** in people who have drank unpasteurised milk from infected cattle.

There is strong evidence that disease occurs after the organism is inhaled. Healthy persons with exposure to ***cryptococcus*** have a much higher rate of positive ***cryptococcal*** skin tests but no cases have been recorded in clusters, no occupational predisposition or person to person transmission has been documented.

Most cases of ***cryptococcal*** infections are caused by serotype A and D strains while serotype B and C are responsible for a significant number of infections in tropical and subtropical areas of the world. The ecological site of B and C serotype remains unknown to date.

d. Factors predisposing to infection.

It seems that human beings have a very high level of natural immunity to the ***cryptococcus*** but there does seem an increase in the incidence of the disease in those with the following conditions:-

i) Acquired Immunodeficiency Syndrome

ii) Lymphoreticular malignancies such as leukemias and lymphomas.

iii) Sarcoidosis

iv) Diabetes Mellitus

v) Those on immunosuppressive drugs such as transplant patients.

There seems to be another variety of ***cryptococcus*** which occurs in immuno competent individuals.

e. Diagnosis

Cerebrospinal Fluid findings (CSF)

There are usually no major abnormalities in hematocrit, sedimentation rate but there are almost always changes in cerebrospinal fluid. Detection of organism by culture is necessary for diagnosis but smears using indian ink are very necessary as well. Nigrosin ink is also very important and in fact distinguishes ***cryptococcus*** from many artifacts. Gram stains and cytological studies are not very helpful and findings may be misleading.

Urine and sputum cultures must be done though the yield is generally poor. Blood cultures must be performed as possibilities of positive yield are more likely with disseminated infections such as those with Acquired immunodeficiency syndrome (AIDS).

Serological tests are also available but detection of the ***cryptococcal*** polysaccharide capsular antigen is the only procedure that is useful clinically though positive cultures are still the cornerstone for diagnosis.

PATHOPHYSIOLOGY

Pathology

Cryptococcus exhibits no known toxins. Most of the pathology observed is due to tissue invasion by multiplying organisms but no necrosis or organ dysfunction has been observed until late in the course of the disease when the fungal burden (load) is very heavy.

Haemorrhage, infarction, calcification, extensive fibrosis and strong inflammatory response are lacking though minimum response may be observed.

Outside the central nervous system and to some extent in the meninges, macrophages and giant cells may be observed but with no granuloma formation though these cells contain ingested ***cryptococci***. Some inflammatory infiltrates are of mixed cell types though neutrophils may predominate. The predominant or characteristic lesions seen in the brain or elsewhere consist of cystic clusters of fungi with no inflammatory response that are widespread all over the brain.

Typically the basal ganglia and cortical grey matter are involved and there may sometimes be formation of large clusters of fungi forming a ***cryptococoma*** though this is a rare phenomena. Leptomeninges are often thickened with distention of the subarachnoid by a white, gelatinous material attributed to the poly saccharide capsule.

Cellular host defence mechanism

There does seem to have accumulated strong evidence that an integration of a number of cells such as neutrophils, lymphocytes and macrophages is responsible for strong host resistance to ***cryptococcus***. Human neutrophils and monocytes can ingest and kill ***cryptococcus*** while activated macrophages also ingest the fungus. Besides the above cells, sensitised T cells and natural killer cells also play a very important role. While these cells seem to be important in clearing the fungi, there is no proven evidence that defects in the functioning of these cells result in increased cases. ***Cryptococcal*** cell wall is capable of activating the alternate complement pathway.

Cryptococcal Polysaccharide **versus host immunity**

This capsule has been shown to be immunosuppressive in the host. Long after being cured of ***cryptococcosis***, patients may exhibit prolonged unresponsiveness to the antigen. This polysaccharide capsule also seems to inhibit phagocytosis by binding to the yeast surface and blocking phagocytosis. The capsule may impair leukocytes kinesis and may activate alternative complement pathway.

Humoral Host Defense

Though ***anti-cryptococcal*** antibody and complement do not lyse the organism directly, there are critical factors in the functioning of the cellular immune response. There are other factors present in serum which are not present in the central nervous system (CNS) and may explain why we tend to get predominant CNS manifestation.

1.3 LITERATURE REVIEW

a. The setting

Cryptococcal meningitis is probably the most important life threatening fungal complications of AIDS though it was first reported in 1916 in the USA (Stoddard and Catler) well before the AIDS pandemic.

It used to be a predominantly male disease and occurred in most patients who were immuno-compromised in one form or the other though its other variety ***cryptococcus*** neoformans var gatti occurs in immunocompetent people.

Its world incidence or prevalence is unknown though it is estimated that between 6% and 10% of patients with AIDS will develop central nervous system infection with ***cryptococcus***. This has strongly been supported by Kovacs JA, Kovacs AA et al (Ann International Med., 1985) who have clearly demonstrated a parallel increase in the number of cases since the advent of AIDS. There has also been a similar increase in Central and West Africa. (Richard, Mohomadas and Arugamasamy, 1976; Tija and Tan 1985; Gould-Gould, 1985). While generally it is an indisputable fact that there are more cases in situations of lowered Immunity (Pathoello-Montovani et al 1992), Schmutzhard et al 1989 found less association between a low immunity and ***cryptococcosis***. This theory of immunocompetence with ***cryptococcal meningitis*** is supported by reports from Papua New Guinea where ***cryptococcal meningitis*** occurs predominantly in immunocompetent individuals. In contrast to other countries, in New Guinea, it occurs

in young, previously healthy, adults and children who have no evidence of underlying human immunodeficiency virus (HIV) infection or other causes of immunosuppression (Seaton et al 1995, 1996b)

It is generally agreed that of the two varieties of ***cryptococcus*** i.e ***Cryptococcus neoformans var neoformans*** and ***cryptococcus neoformans var, gatti*** the former occurs in immuno-deficient states while the latter as in Papua New Guinea may occur in immunocompetent people (Kovacs et al 1995). It is therefore, the duty of every country to identify the setting in which ***cryptococcus*** occurs.

b The clinical features

The clinical presentation of ***cryptococcal meningitis*** is quite vast and hence the problems encountered in making the diagnosis cerebral ***cryptococcosis*** is the most common form of presentation (Chuck S.L, 1989) usually presenting as chronic headache, nausea, vomiting, staggering gait, dementia, irritability, confusion and blurred vision. Fever and nuchal rigidity may be absent. Papilloedema is present in about one third of patients (Andre R. Seaton et al, 1996).

Focal or generalised convulsions have also been reported (Lipton et al, 1991). Many researchers agree that together with ***cytomegalovirus***, ***tuberculosis*** and ***toxoplasmosis***, ***cryptococcus*** is one of the leading causes of headaches in immuno-compromised individuals. Pulmonary ***cryptococcosis*** with chest pains has been demonstrated usually at autopsy and accounts for about 40% of cases. Some 20% of patients may present with a cough. Calcification, pleural effusions, cavitation and fibrosis are rare.

Bisseru et al (1983) reported the first Zambian case of pulmonary ***cryptococcus*** in a 19 year old Zambia man who had looked after pigeons. Earlier, in 1969 Bhagwandeen, Zambia, had reported a case of disseminated ***cryptococcosis*** and later on Patel K.F. (1977) reported a case of tracheal obstruction in a Zambian patient.

Skin lesions (Chuck S.L. et al 1989) are reported in 10% of patients.

Rex et al (1989), in their article on catastrophic visual loss mentioned iritis, choroiditis and retinitis. Rare manifestations include osteolytic bone lesions, cold abscesses, prostatitis, endopthalmitis, pericarditis, endocarditis and renal abscess.

c. Laboratory

John E Bennet et al, (1984) summarises the CSF laboratory findings as being very low sugar, high protein, low chloride and very high lymphocytes in immunocompetent patients and a variable laboratory finding in immuno-compromised patients.

d Therapy

William G. Powderly from Division of Infectious Diseases in Washington (1996) sums it up as follows; "treatment of ***cryptococcal meningitis*** once difficult, has become much clearer as a result of carefully controlled trials in the last few years and there is probably little debate about standard therapy at this point." Most clinicians would start with Amphotericin B in the initial therapy and probably would add flucytosine and maintain their patients on an azole."

There are other issues such as the ones raised by Sharkey et al Witt et al (1996), namely, "can we use an azole as initial therapy and does the toxicity of amphotericin B warrant seeking alternative treatment.?" Although such regimes are advocated as is the practice at the University Teaching hospital now, it is very clear form prospective randomised trials that only 50% will respond if treated with a triazole, (Saag MS, Powderly et al (1992). Furthermore, it has not been possible to identify prior to therapy which patients would respond.

The trial by Witt et al (1996) attempts to identify patients who would best respond to Fluconazole and they found that the fungal burden, ***cryptococcal*** susceptibility to Fluconazole and concomitant use of Flucytosine as predictors of a response. Thus we are not debating the use of Fluconazole alone but combination chemotherapy. Flucytosine alone has been shown not to be effective because of the emergence of resistance strains.

Review of current data about the role of Amphotericin B in the management of AIDS associated ***cryptococcal*** meningitis by the mycosis study group and AIDS Clinical Trial Group shows that the use of high dose Amphotericin B (0.7mg/kg for first 2 weeks) is associated with an acute mortality of 6% and an overall response rate of 60%-70%. This short course of amphotericin B was apparently well tolerated.

The controversy does not end, Marinka Kartalija et al (1996) from San Francisco USA, initial advocates of Fluconazole now recommended that therapy be initialised with amphotericin B for 10 -14 days after which patients could then be switched to Fluconazole. Alternatively, it is generally accepted that Flucytosine be combined with Fluconazole initially after which patients could be maintained on Fluconazole alone.

d. Recommended therapy

i Recent evidence indicates that a combination of amphotericin B and Flucytosine is as effective as amphotericin B alone and should be the treatment of choice for ***cryptococcal*** meningitis. Compared with amphotericin B given at 0.4mg/kg/day this combination cured more patients, sterilised CSF more rapidly and was less nephrotoxic. The recommended dose is amphotericin B 0.3mg/kg body weight per day and Flucytosine 37.5mg/kg body weight every 6 hours by mouth for six weeks. Relapses are very common in AIDS patients and the therapy may have to be continued for a long time or maintenance Fluconazole in dosage of 200mg/day by mouth may be used.

Amphotericin B

ii If above combination cannot be given to a particular patient intravenous amphotericin B at 0.4-0.6mg/kg/day (or double the dose) on alternate days may be used. Early toxicity is managed by adjusting the dose and administering low dosage corticosteroid.

Fluconazole (azoles)

iii At dosages of between 200-400mg/day, now shown to have more benefit after acute treatment or in combination with Flucytosine in the initial therapy.

Flucytosine

iv Of very little use if used alone because of the emergence of resistance strains. Best combined with amphotericin B or Fluconazole.

THE ZAMBIAN BURDEN

With the coming of the Acquired Immunodeficiency Syndrome (AIDS) on the Zambian scenario (officially 1986), there has been an exponential increase in the number of cases of tuberculosis (Banda J.S, Elliot, Mwiinga et al 1993), Kaposis Sarcoma, multidermatomal herpes zoster, oral candidiasis and the deadly ***cryptococcal*** meningitis.

When Bhagwanden (1969) reported the first Zambian case of disseminated ***cryptococcosis***, little did he realise that 36 years later, ***cryptococcal*** meningitis was going to be the leading cause of meningitis in Zambia (UTH). Other reports of ***cryptococcosis*** came from Susha Carruthers 1977 and Bisseru in 1983.

Perera and Mulenga (1993) were the first to alert the clinicians about the increase in the incidence of ***cryptococcosis*** in the laboratory data. They attributed this increase to the AIDS pandemic which was just beginning to have its toll on the Zambian soil.

Between 1989 and 1991, a total of 163 cases were isolated at the University Teaching Hospital alone and the figure further shot up to 188 in 1994 alone. In 1995 a total of 231 cases were isolated and during 1996 the number further shot up to 367 during the period from December 1995 to December 1996.

Cryptococcal meningitis has thus become the leading cause of meningitis at the University teaching Hospital surpassing the traditional causes such as streptococcal pneumonia and neisseria meningitides (See charts on next 3 pages).

TABLE 1. The five leading causes of Meningitis, 1995-1996

	1995	1996
CRYPTOCOCCUS NEOFORMANS	231	367
PNEUMOCCOCAL MENINGITIS	205	245
NEISSERIA MENINGITIDIS	85	86
HAEMOPHILUS INFLUENZAE	17	20
E. COLI/	20	22
SALMONELLA SUB-TYPES	28	62

Figure 1

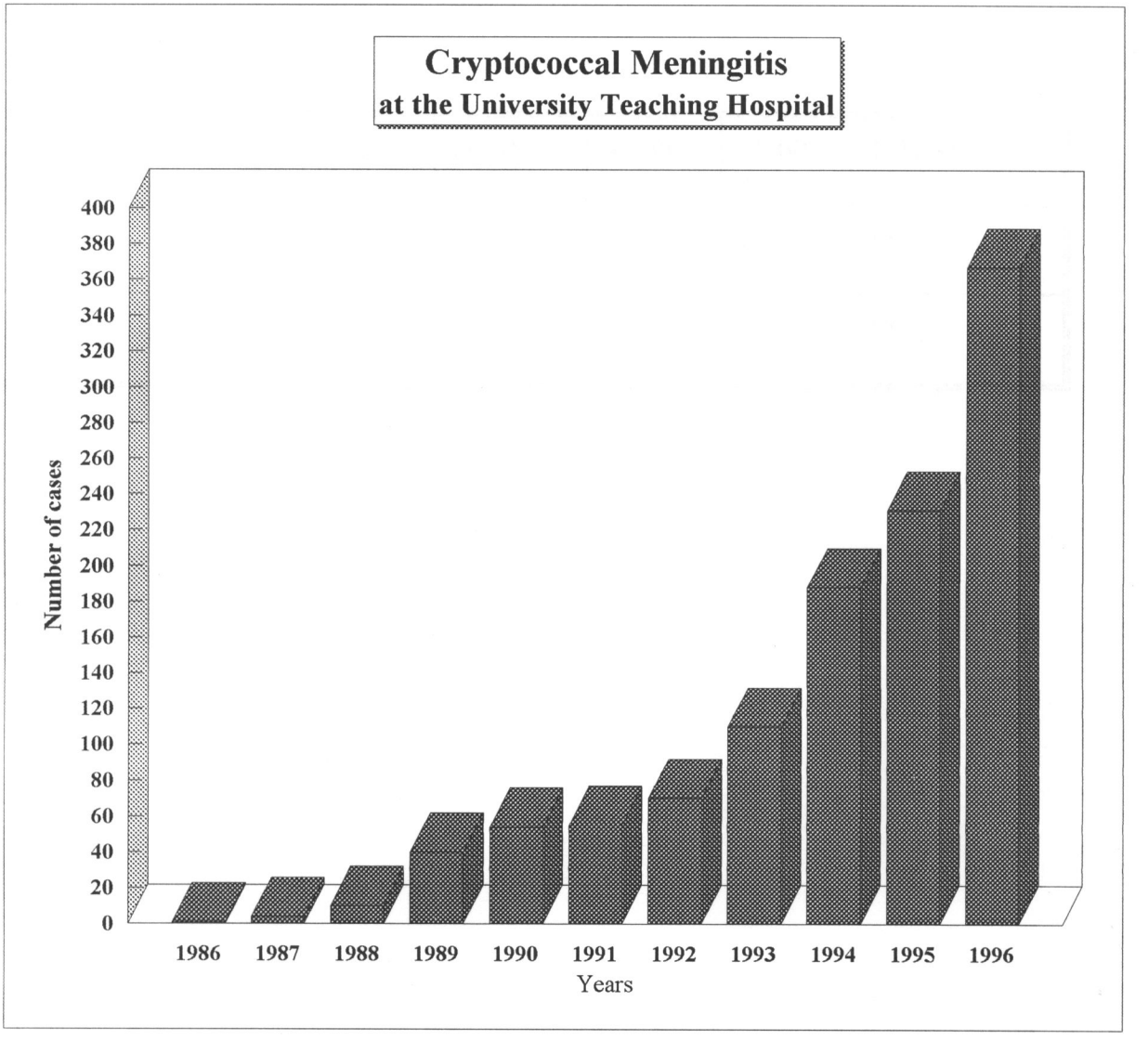

Cryptococcal Meningitis
at the University Teaching Hospital
Number of cases
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
Years

TABLE 2: Sex distribution for Cryptococcus - 1996

SEX	15-25	26-35	36-45	46-55	56-60	TOTAL
Females	86	59	31	3	1	180
Males	7	43	120	10	10	187

Attempts by previous researchers at the University Teaching Hospital to define the clinical setting of the patients were first made by Mwansa and Tembwe who were handicapped by a small sample size as they were just trying to retrieve the files of the patients whose CSF laboratory results were positive for ***cryptococcus***. Among the common symptoms they noted were headache, vomiting and weight loss but they could not tell whether the patients were immuno-compromised or not.

Cryptococcal meningitis is fatal without proper therapy and going at the rate at which we are seeing this kind of patients, there is urgent need to evaluate the efficacy of the drug (fluconazole) being used. Our problems are compounded by lack of the antigenic kit for both early diagnosis and monitoring of treatment.

1.5 OBJECTIVES OF THE STUDY

1 To assess the clinical setting of ***cryptococcal*** meningitis at University Teaching Hospital.

2. To determine the prevalence of ***cryptococcal*** meningitis and compare it with other meningitides

3. To test the efficacy of Fluconazole as prime therapy in the treatment of ***cryptococcal*** meningitis and other associated fungal infections at University Teaching Hospital.

4. To define the laboratory features of ***cryptococcal*** meningitis.

2. MATERIALS AND METHODS

This study was conducted at the University Teaching Hospital in Lusaka, Zambia, a central African state with an estimated population of 9.458 million people. Lusaka alone which is the capital city of this mineral rich country, has a population of 1.206 million and is very heavily urbanised with mushrooming of shanty compounds on an uncontrollable basis. (Central Statistics Office: Population projections 1990 Census database)

Zambia, a tropical country is 1067-2350 meters above sea level, has a hot season from October to March, cool dry season from May to August and temperatures may range from 26.7°C to 32°C though they may drop to as low as 13.4°C at times.

Zambia is one of those very heavily urbanised countries and has more than half its population, which is mainly Bantu in ethnicity in urban areas. This has resulted in congestion in towns and a stress on water supply and other services such ass medical supplies.

The University Teaching Hospital is the only major hospital in this city and is also the country's most specialised and referral hospital (tertiary). It has a bed capacity of 1,800 though these have been extended as "floor beds" may appear depending on the need. There are about 430 medical ward beds.

The country has been undergoing a serious economic crusade and has entered on a structural adjustment programme which is donor driven. Its gross domestic product has significantly dropped and per capita income is less than 185 United States Dollars.

This scenario has been worsened by the increase in the poverty related diseases such as malnutrition, Tuberculosis etc while the impact of HIV has worsened the problem.

2.2 PATIENTS SELECTION AND EXCLUSION

A prospective longitudinal study conducted at the University Teaching Hospital from December 1995 to December 1996.

Three hundred and sixty seven patients were seen during the study, one hundred and thirty of whom fulfilled the following:-

a. Inclusion criteria

- Above 15 years and coming from Lusaka
- Non pregnant
- Cerebrospinal fluid proven ***cryptococcal*** meningitis (culture positive)
- prepared to buy own Fluconazole of 200mg after 6 weeks of therapy.
- consent
- Normal liver and kidney function
- Not on any other anti-***cryptococcal*** therapy prior to commencement of therapy.

b. Exclusion Criteria

- Under 15 years
- pregnant
- Presence of other causes of meningitis in cerebral spinal fluid.
- Having taken other anti-fungals such as amphotericin B prior to diagnosis.

- Critically ill from other disease other than ***cryptococcal*** meningitis.
- no consent
- abnormal liver function tests or urea electrolytes

c. **Discontinuation from the Study**

- Severe side effects from drugs such as very high liver enzymes.
- Patients voluntarily quitting the study

Recruitment of patients

Out of three hundred and sixty seven patients with cerebral spinal fluid proven ***cryptococcal meningitis*** seen during the period, one hundred and thirty patients were eligible for study and recruited. The reminder of the patients were followed up by their respective units except for one hundred patients who were followed up as controls. (These could not afford the subsequent therapy after 6 weeks and had agreed to be followed up for analgesia and other supportive therapy).

At presentation a detailed history, physical and laboratory evaluation was done. Addresses and maps of areas of residence including postal addresses were taken. The patients upon discharge were also attached to the home based care and a review date given to them upon discharge where this author reviewed each and everyone of them. If patient defaulted for follow up, the patients were physically followed at the address previously given and outcome and compliance recorded.

2.3 Epidemiological features

1. Age - last birthday
2. Sex
3. Marital status recorded as - married, widow/widower, divorced, or single.
4. Profession
5. Number of years in school - primary, secondary, or college.
6. Residential and postal addresses - Classified as high and low density.

2.4 Clinical features

These included complaints at admission, duration of symptoms (acute or chronic), and included such things as :

i. Headache
ii. Fever
iii. Vomiting
iv. Seizures
v. Slowness in thought
vi. Weight loss
vii. Cough
viii. Skin complaints

Other details sought included, Drugs taken prior to admission, past medical history with emphasis on tuberculosis, herpes zoster, kaposis sarcoma and immunosuppressive diseases such as cancers and diabetes mellitus.

A thorough clinical examination was done with emphasis on

a. General body weight and general examination
b. Malnutrition
c. Mucocutaneous manifestations such as fungal nails, oral ulcers pruritis etc.
d. Herpes Zoster scar
e. Oral candidiasis
f. Lymphadenopathy whether localised/generalised
g. Herpes simplex
h. Meningeal signs
i Cranial nerve palsies
j. Level of consciousness
k. Motor and sensory assessment.

2.5 Laboratory

1. Cerebral Spinal Fluid (CSF) - All culture positive

   a. Colour

   b. Pressure as observed (No manometer and therefore not reliable)

   c. Cell counts - polymorphs - High, Low, normal

      - Lymphocytes- High, low, normal

   d. Biochemistry - Sugar - Normal, low, High

      - Protein - normal, low, high

      - Chloride - normal, low, high

e. At six weeks of therapy and at 12 weeks, a to d repeated.

2. CD_4 counts

   a. Greater than 200

   b. Less than 200 and above 100

   c. Less than 100

3. HIV Test - Anonymous unlinked in all patients

4. Full Blood count and ESR

5. Malaria Parasite

6. Liver function test at start, 6 weeks and 12 weeks and monitored every month on treatment. Similarly, urea and electrolytes was also done.

7. Chest X-ray at start or if patient complained of chest symptoms during therapy.

The patients were followed up during admission and at 2 weeks post discharge but major evaluation was at 6 weeks and 12 weeks there after monthly. They could however be seen whenever they felt unwell.

8. Statistics

All the data was entered into a computer and was later analysed using the Epi info,

9. Drugs: All patients were commenced on Fluconazole 400mg start and then 200mg once a day for the duration therapy. The route of administration was oral or intravenous depending on condition of patient

The patients were also treated for concomitant infections such as enteritis or indeed tuberculosis.

RESULTS

A total of one hundred and thirty patients was seen during the study from December 1995 to December 1996 and another hundred patients were followed up as controls. During this period, a total of three hundred and sixty seven patients had been diagnosed as having ***cryptococcal*** meningitis.

HIV serotyping was done anonymously unlinked on all patients entered in the study and whenever possible, CD_4 counts were also done and a small number of post mortem was done too.

3.1 Age and sex distribution

Of the total number of ***cryptococcal*** meningitis seen, there were one hundred and eighty (180) females and one hundred and eighty seven (187) males bringing the prevalence ration of 1:1.

However of those patients who were eligible for study there were seventy (70) females (53.8%) as opposed to sixty (60) males (46.2%).

Figure 2

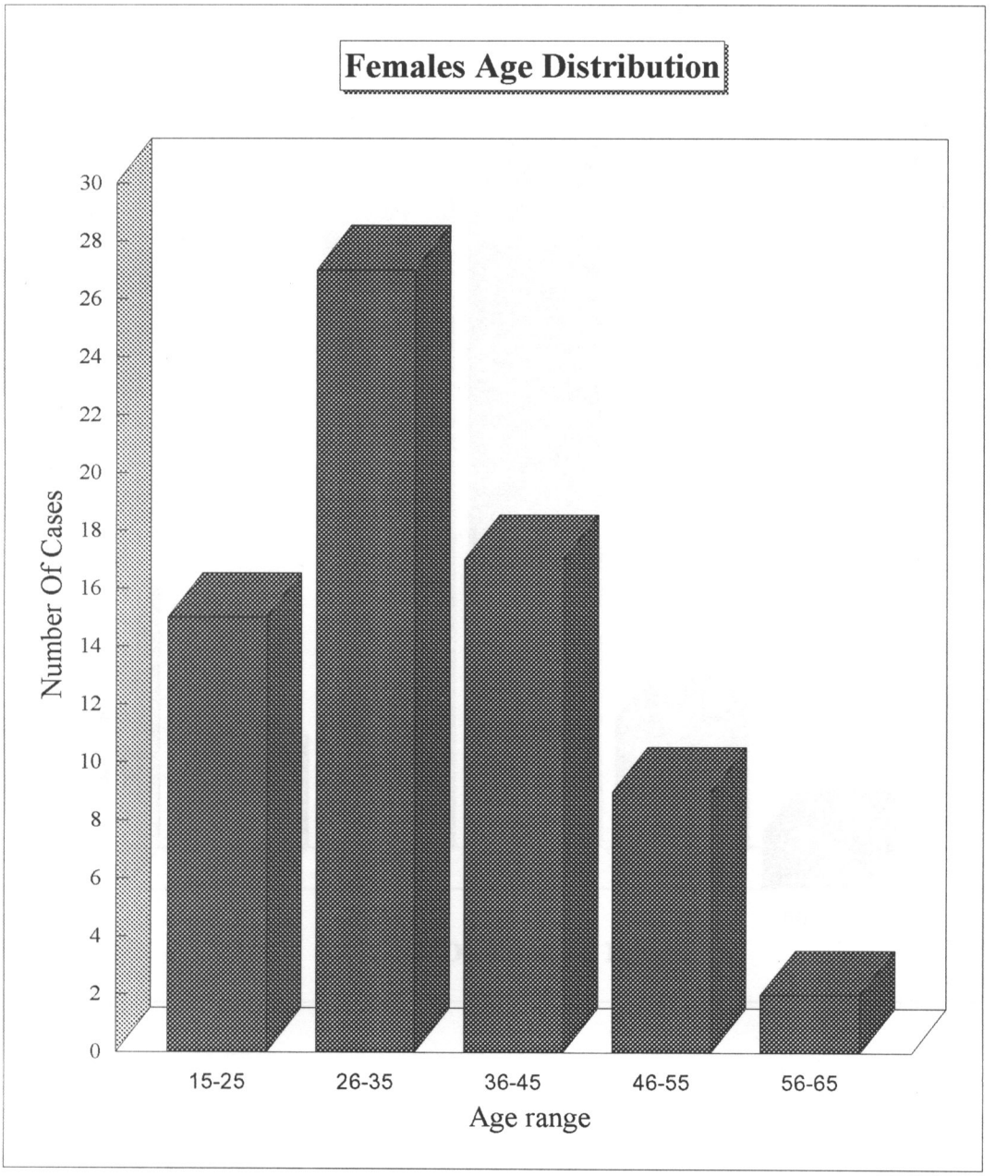

Females Age Distribution
Number Of Cases
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
15-25
26-35
36-45
46-55
56-65
Age range

Figure 3

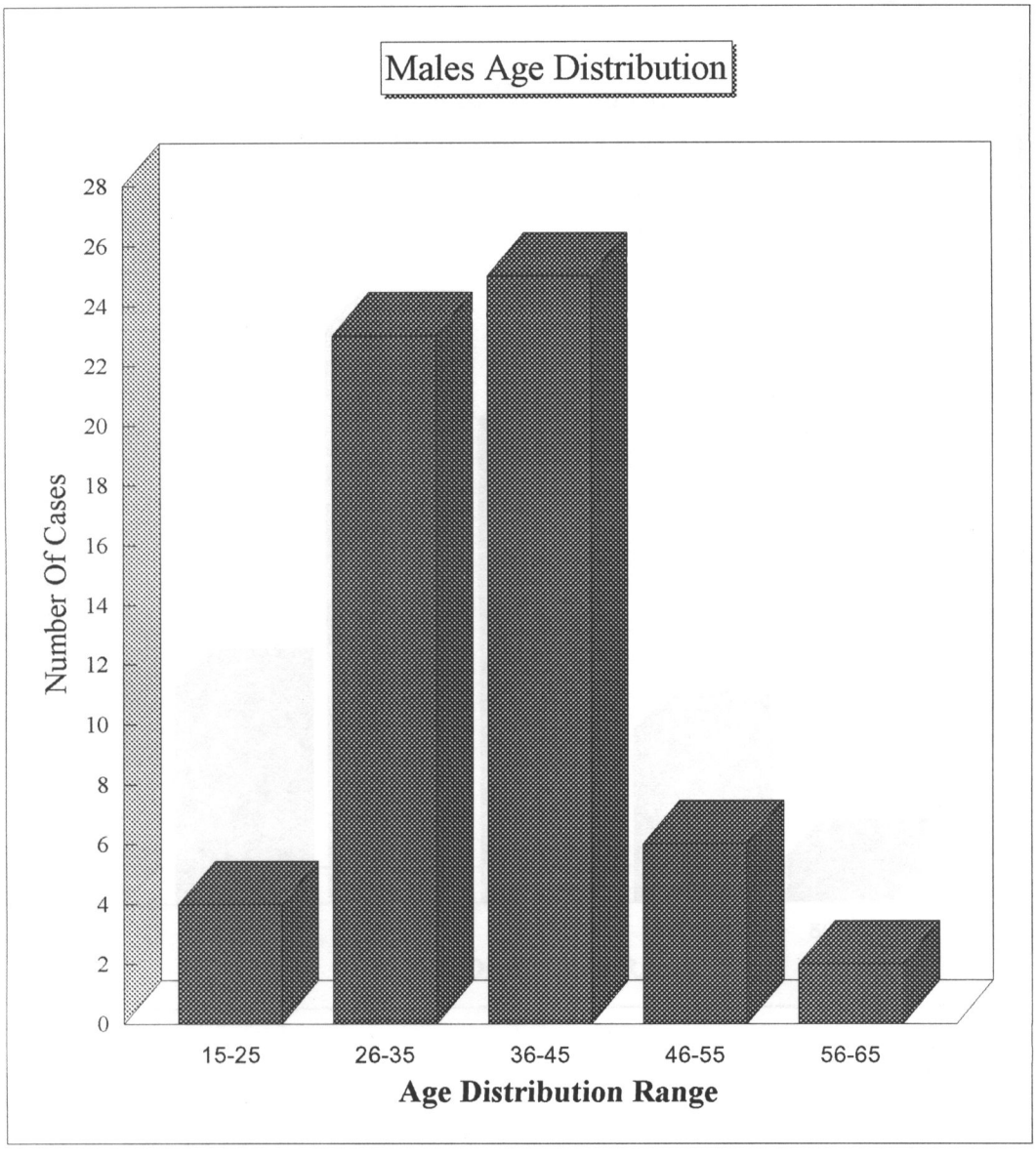
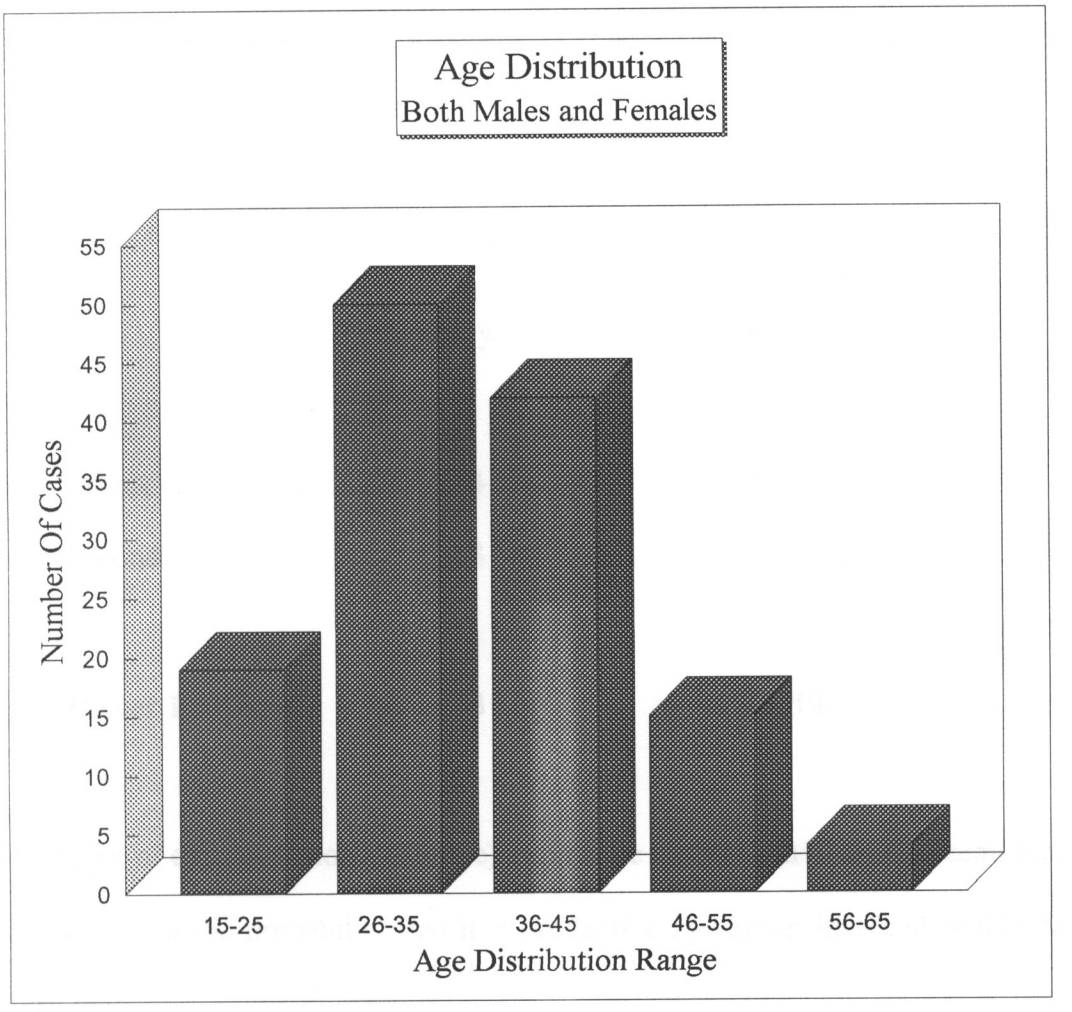

Males Age Distribution
Number Of Cases
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
15-25
26-35
36-45
46-55
56-65
Age Distribution Range

Figure 4


Age Distribution
Both Males and Females
Number Of Cases
55
50
45
40
35
30
25
20
15
10
5
0
15-25
26-35
36-45
46-55
56-65
Age Distribution Range

3.2 Level of Education

The level of education was grouped as either primary, secondary or higher education/college.

	Frequency	Percentage
Primary	34	26.2%
Secondary	43	33.1%
Higher Education	53	40.8%

The number of educated people (literate) seem to be higher than illiterates (semi literate). This means that the probability that it is productive age group involved in this disease is very high.

3.3 Marital Status

Fifty eight, (45%) patients were married . Widowed patients were 31 (24%) while single patients who were mostly females were 37 (28.7%). The number of divorcees was 3 (2.3%).

3.4 Social and Employment

There were 40 people in formal employment, ninety were either unemployed or self employed. The professions were varied and it was impossible to group them into one big family. Ninety percent of the patients were from the high density areas of Lusaka and this was statistically significant.

3.5 Symptoms at presentation.

The main symptoms were headache 119 (91.5%), weight loss 116 (89.2%) others which included a lot of small complaints like perpetually running nose, nausea, abdominal pains etc. 79 (60.8%), fever 67 (51%) but when the actual temperature was taken, most patients had a low grade fever and the figure was much higher. Other important symptoms included mental changes such as forgetfulness, 64 (49.2%), and slowness at answering 63 (48.5%). Itching skin occurred in 51 (39.8%) of the patients.

The average duration of these symptoms is shown in figure 3.5a.

Past Medical History

a. Of all the patients seen 47 (36.2%) had a history of tuberculosis.

Distribution of Tuberculosis.

1. Past - 23 (17.6%)
2. Present - 19 (14.7%)
3. Relapse - 5 (3.9%)

Those with tuberculosis were stable patients in so far as the disease was concerned. Twenty two (16.9%) had pulmonary while twenty five (19.2%) had extra pulmonary tuberculosis of the total number of those who had tuberculosis.

b. Kaposis Sarcoma - Twelve (9.2%) had kaposis sarcoma but not a major problem at time of presentation.

c. Herpes Zoster - Twenty five (19.2%) had herpes Zoster in the past.

d. Diabetes mellitus and other suppressive states other than HIV. One diabetic patient and five patients on steroids from skin clinic for chronic skin condition.

e. **Treatment prior to admission**

A total of 128 (98.5%) had received treatment prior to admission for presenting symptoms.

92 (70.8%) had received anti malarial while 69 patients (53.1%) had taken antibiotics and a further 44 (33.8%) had received different types of treatment.

Note that the same patient could have taken all three.

Table 3.5a **TABLE OF SYMPTOMS OF PATIENTS SEEN**

SYMPTOMS	FREQUENCY	PERCENT	MEAN DURATION(days)	P- VALUE
Headache	119	91.5%	21	< 0.05
Vomiting	47	36.2%	7	< 0.05
Fever	67	51.5%	14	< 0.05
Diarrhoea	12	9.2%	42	> 0.05
Confusion	17	13.1%	5	< 0.05
Forgetfulness	64	49.2%	32	< 0.05
Slowness	63	48.5%	28	< 0.05
Social withdrawal	20	15.4%	4	> 0.05
Seizures	12	9.3%	6	> 0.05
Paralysis	4	3.1%	14	> 0.05
Weight Loss	116	89.2%	30	< 0.05
Itchy skin/rash	51	39.8%	14	< 0.05
Others	79	60.8%	10	< 0.05

3.6 SIGNS AT PRESENTATION

Most of the patients were chronically ill looking, wasted pale, thin silky hair with mucocutaneous manifestation of HIV. Other than the general features of chronic ill health the following were dominant in most patients evaluated; patients generally had low grade fever 90.8% though this was higher than they had mentioned, most of them 89.2% had evidence of weight loss and majority 77.1% had anaemia (pallor). Meningeal signs were present in 84.6% with 77.7% having some neck stiffness and 66.9% with a positive kernigs signs. Another category of patients had rash in different forms of 57.7% and similar figures for oral candida.

Most of the patients had weakness 59.2% though most had a near normal level of consciousness at presentation 86.9%.

For the rest of the signs, check table 3.6a.

Table 3.6a SIGNS AT PRESENTATION

SIGNS	FREQUENCY	PERCENT
Weight loss (wasting)	116	89.2%
Malnutrition	47	36.2%
Fever (temperature high)	118	90.8%
Rash	75	57.7%
Oral Candida	75	57.7%
Anaemia	87	77.7%
Lymphadenopathy	63	48.5%
- Cervical	15	11.5%
- Inguinal	1	0.8%
- General	47	36.2%
Herpes Zoster Scar	25	19.2%
Meningeal Signs	110	84.6%
Neck stiffness	101	77.7%
Kernigs sign	87	66.9%
Photophobia	60	42.6%
Level of consciousness		
- Confusion	17	13.1%
- Alert	113	86.9%
Cranial Nerve Palsies	17	13.1%
- 6^{th}	12	9.2%
- Others	6	
Funduscopy - Papilloedema	24	18.5%
Motor Impairment		
- Normal	77	59.2%
- Weakness	52	40.0%
- Plegias	1	0.8%
Sensory		
- Normal	106	81.5%
- Impaired	24	18.5%

3.7 LABORATORY FEATURES

1. Cerebral Spinal Fluid (CSF)

a Normal
- Cells 5/mm^3 lymphocytes
- Glucose 2.5 - 4.0mmol/l
- Protein 100 -400mg/l
- Pressure 5-15cm CSF

b. Pressure - Though 90.8% of patients had high pressure, it is difficult to comment as no manometric studies were done. The reported pressure was as seen when CSF came out of the needle!

c. Colour, Protein, Sugar and Cell Count

COLOUR	%	MEAN PROTEIN Mg/L	MEAN SUGAR mmol/L	MEAN CELLS /MM^3
CLEAR (70)	53.8	550	1.5	5
TURBID (52)	40	1550	1.0	14
XANTHOCHROMIC (8)	6.2	2000	1.7	17

As the majority of the patients died under six weeks, it was not possible to do serial CSF studies.

In a small sample of twenty in this study the following chloride results were done.

e. Chloride (20 patients)

Normal	-	2(116-130mmol/l) = 10%
Low	-	15(mean 82mmol/l) = 75%
High	-	3(mean 132mmol/l) = 15%

2.) CD_4 Counts

Using both the Zambart and JICA projects, only thirty patients had CD_4 counts done.

Greater than 200	-	5 = 16.67%
Less than 200	-	25 = 83.33% mean 86.

Using these counts as standard, it is quite clear that patients fulfilled the criteria of diagnosis of AIDS.

3.) Anonymous unlinked HIV test in 130 patients.

Of the 130 samples screened, 125 were sero-reactive for HIV I and II representing a seropositive rate of 96.15%. These were unlinked and therefore it was difficult to identify the 5 who were seronegative but could be those on steroids and the diabetic.

4.) Full Blood Count and ESR

- Anaemia of chronic illness, normocytic, normochromic was found in 87 out of 130 patients representing 77.7% of patients.

- Leukocytosis - only 41 (36.6%) of the patients had leucocytosis.

- Leukopenia - 46 (41.1%) had leukopenia

- Erythrocyte Sedimentation rate
  - 107 (96.4%) of patients had a raised sedimentation rate with a mean of 45mm/hr.

5. Malaria Parasites

- Only 7 patients (5.7%) had malaria positive slides.

6. Liver function test - urea and electrolytes

These were a prerequisite to being included in the study and therefore they had to be normal. During the course of the study only 4 (3.08%) had shown an elevation of liver enzymes to about twice the normal and this did not warrant the stopping of treatment. The drug was otherwise very well tolerated.

7. **Chest Radiographs**

As reported by the radiologists:-

1. 22 - Old calcified nodes (hilar) no active (16.92%) lesions seen.

2. 15 - Right/left basal infiltrates with (11.54%) hilar lymphadenopathy. Tuberculosis can not be excluded.

3. 10 - Active tuberculosis (7.69%).

4. 13 - Non specific interstitial pneumonitis. Exclude infections or retroviral disease.

5. 70 - Normal Chest X-ray. (53.84%).

3.8 POSTMORTEM FINDINGS

It was felt half way through the study that looking at post mortem findings would probably yield more information on the disease. Due to failure to obtain consent for a full post mortem especially that most patients and relatives had already been counselled. Only ten postmortems were done.

Results: Clusters of ***cryptococci*** identified in brain tissue, non-specific cell infiltrations mainly lymphocytes and polymorphs. No granuloma formation. No or mild vasculitis and no other findings. Similar findings in other organs such as the liver and spleen.

3.9 OUTCOME:

Of the one hundred and thirty patients studied, nine, 6.9%, were still alive by December 30th, 1996, while one hundred and seven (82.3%) had actually died and there were fourteen (10.8%) whose outcome was unknown because they had actually gone off to the villages or out of town or proved difficult to trace.

Of those that were alive, four were males while five were females and here below were their specific features:

a. Headache - All of them had this and there was no major difference between the group that died in terms of duration of symptoms.

b. Vomiting - None of the alive patients.

c. Fever - Seven of the nine patients.

d. Diarrhoea - None of them.

e. Confusion and mental changes None of them.

f. Lymphadenopathy - Six of the nine patients had generalised lymphadenopathy while three had none.

g. Tuberculosis - None of them had tuberculosis either in the past or presently.

h. Cerebral Spinal Fluid - The CSF was mainly clear (66.7%) as opposed to a turbid CSF in 33.3%.

i. CD_4 - Of the six who had CD_4 in this group, their average was 150 as opposed to the majority of the patients who had average 86.

j. Full Blood Count - Except for one who had anaemia of chronic infection, the rest of the patients had normal blood counts.

Other than the above features, these patients generally had no stigmata of chronic ill health.

The distribution of deaths was as follows.

WEEKS	
1 - 6	intensive phase = 79 (73.8%)
7 - 12	11 = 10.3%
13 - 18	10 = 9.3%
>19 weeks	7 = 6.5%

It is quite clear that the mortality was quite high in the intensive phase as compared to the other periods. Outcome for the untreated group (100) who could not afford treatment.

Unknown - 12 = 12%

Brought in dead from home - 20 but died in less than 6 weeks.

Died in the hospital - 54 died in under six weeks.

Total number of patients who died of the 88 patients followed up

at 6 weeks 74 = 84.09%

at 12 weeks 14 = 15.91%

By the 12th week, all the patients not on treatment had actually died.

4.0 DISCUSSION

Age and sex

It has become quite clear that ***cryptococcal*** meningitis is a very serious opportunistic infection affecting mainly the young age group. The peak incidence is 26-35 years for females while it is 26-45 years for males. This is similar to the study on tuberculosis and HIV that was done by J.S. Banda (1993). Of the one hundred and thirty patients looked at, one hundred and seven were actually below the age of 45 years (82.31%). This may not mean that this is the most vulnerable group but may actually be a reflection of the fact that most of the Zambian population falls in that age category. The fact that the male to female ratio seems to be equal (from the three hundred and sixty seven patients seen, does to a greater extent suggest that the disease is related to the acquired immunodeficiency syndrome.

Marital status

The surprising thing that came out of this study was to why married people tended to have the disease more than the single, divorced or widowed. Could this suggest infidelity or could it be that people get married to have someone to look after them knowing very well that they are already sick? In fact, most of the marriages were under five years old! The widowed and the single at 24.0% and 28.7% respectively compared very well and could probably explain the fact that the widowed later on behave like singles.

The clinical syndrome though vast in this study, does point to one thing; there is a very strong bond between this disease and human immunodeficiency virus at least in the Zambian setup. It is also surprising that 75% of these patients had either secondary or

college education despite such a high prevalence of HIV in the group. It raises the serious issues of knowledge and attitudes.

Presentation and Clinical features

Cryptococcal meningitis presents as a chronic headache with a mean duration of 21 days and was present in 91.5% of the patients. Majority of the patients had lost weight (89.2%) (something that can be attributed to the high sero-prevalence in this group) and a fever was present in 51% of the patients. Mental changes and forgetfulness were also a common feature. It is worth noting that the majority of the patients also had features of chronic ill health such as candidiasis, herpes zoster and Kaposis sarcoma. Pruritic skin rash was also a feature in most patients and a good number had tuberculosis either at presentation or in the past. These symptoms were comparing favourably with figures from Sub-Saharan Africa Maher D et al (1994) where ***cryptococcal*** meningitis is on the increase though they seem to be different from features from Papua New Guinea where ***cryptococcal*** neoformans gatti seems to be associated with more severe ocular manifestations (Seaton et al 1995). There is also a high occurrence of papilloedema (in 33% of patients according to Mitchell et al 1995) as opposed to Zambian patients where papilloedema occurred in only 18.5% Visual loss did not occur in any of the patients in this study while other authors have estimated it to be 1.1% in infections with ***cryptococcal*** neoformans neoformans (Rex et al, 1993). From the behaviour of our ***cryptococcal*** meningitis patients, it is quite clear that we are probably dealing with the species neoformans neoformans though confirmation by appropriate serological tests is required.

The striking laboratory feature of this disease was its strong similarity with pyogenic meningitis in its Biochemistry findings: a high protein and low sugar. Low chloride in those patients that were later analysed clearly demonstrated difficulties that might arise in distinguishing between meningitis due to ***tuberculosis*** or ***cytomegalo*** virus infection.

The Cerebrospinal Spinal Fluid (CSF) is usually clear in the majority of patients with a mean cell protein of 550mg/l and mean sugar level of 1.5mmol/l. There is usually very little cellular reaction. In those patients whose CSF was turbid, the colour seems to be due to a high protein content with a mean of 1550mg/dl with again minimal cellular reaction. This compares favourable with other researchers findings (Benett 1994). The major full blood count finding is an anaemia of chronic ill health; normocytic normochromic which occurred in 77.7% of patients. The sedimentation rate was raised in 96.4% of the patients.

Though majority of the patients had taken anti malarial before admission 70.8%, 5.7% of the patients had positive malaria slides $p > 0.05$. The liver and kidney functions done in most of these patients were normal and there did not seem to be a major increase even at six weeks of treatment (those who got there) suggesting the possibility that Fluconazole is a relatively nontoxic drug. Of all the patients seen, none had sterile cultures at six weeks though 2% had at 12 weeks.

Almost all the CD^4 done in these patients were below 200 and coupled with a very high sero-prevalence for HIV, ***cryptococcal*** meningitis seems to be an AIDS defining illness in our setup in the absence of a demonstrable cause of immunosuppression. This is in tune with CDC (Atlanta) 1993 criteria for AIDS.

In looking at the general outcome in these patients confounding factors such as presence of other viruses or parasites could have increased our mortality though the comparison with the group not on Fluconazole reduced this possibility . It would be better to do another CSF study of patients with ***cryptococcal*** meningitis and look at the prevalence of other opportunistic infections.

5.0 CONCLUSION

In this study which was conducted at the University Teaching Hospital, from December 1995 to December 1996:-

5.1 ***Cryptococcal*** meningitis is now the leading cause of meningitis among the isolated organisms at the University Teaching Hospital Lusaka Zambia and three hundred and sixty seven patients were seen during the period of study.

5.2 Fluconazole as prime therapy in the acute phase of treating ***cryptococcal*** meningitis is NOT EFFECTIVE and therefore there is urgent need to evaluate other modalities of treatment as is the practice elsewhere. However, Fluconazole has a role to play in the treatment of other opportunistic fungal infection where the response was very good. Fluconazole is a very safe drug as no patient developed any serious reactions or elevation in liver enzymes or renal impairment during the period of the study. Fluconazole is thus more important in the maintenance stage as is the case elsewhere.

5.3 The strain responsible is not known but from its clinical behaviour, it seems it is caused by the subspecies ***cryptococcal neoformans neoformans*** and occurs in a state of immunosuppression mainly secondary to the human immunodeficiency virus as is evidenced by a high HIV sero-prevalence and very low CD^4.

5.4 Fever and headache of three weeks standing at least, in a retroviral background setting should alert one to the possibility of ***cryptococcal*** meningitis though the symptomatology is vast.

5.5 The main laboratory findings are those of pyogenic meningitis in biochemistry such as low sugar, high protein, and a low serum chloride. Cerebral Spinal Fluid colour does not seem to help in distinguishing between the different causes of meningitis.

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APPENDIX I

BASIC INFORMATION ON ADULT PATIENT

0. GENERAL

0.1 Sex: (M,F) 0.2 Age: .....y.....m

0.3 Marital Status: married/widower/widow/divorced/single

0.4 Profession:.....

0.5 Residential and Postal Address.....

0.6 Number Of Years in School:primary/secondary/university

0.7 Treatment prior to admission: (Y,N)

1. anti-malaria 2. antibiotics 3. others

0.8 Date of Admission:.....

1. COMPLAINT AT PRESENT

(a)

(b)

(c)

(d)

(e)

(f)

2. PRESENTATION AT PRESENT

2.1 Forgetfulness (Y,N)

2.2. Slowness of thought (Y,N)

2.3 Social withdrawal (Y,N)

2.4 Seizures (P,G)

2.5 Paralysis (Y,N)

2.6 Weight Loss (Y,N)

2.7 Malnutrition (Y,N)

2.8 Chronic Diarrhoea (Y,N)

2.9 Fever (Y,N) for .....weeks

2.10 Persistent cough (Y,N) for .....weeks

2.11 Minor muco-cutaneous manifestation (Y,N)

1. Seborrheic Dermatitis 2. Pruritus

3. Fungal nails 4. Oral ulcers

2.12 Herpes Zoster (Y,N) How many times....

2.13 Oral Candidiasis (Y,N)

2.14 Oral Hairy Leukoplakia (Y,N)

2.15 Chronic and disseminated Herpes simplex (Y,N)

2.16 Lymphadenopathy (Y,N)

1. Generalized 2. Cervical 3. Inguinal 4. Axillary

2.17 Kaposis Sarcoma (Y,N)

2.18 Tuberculosis (Y,N)

1. Present 2. Past 3. Relapse

4. Pulmonary 5. Extra-pulmonary

2.19 Bacterial Infections (Y,N)

1. Sepsis 2. Pneumonia 3. Meningitis 4. Others

2.20 Meningeal Signs (Y,N)

1. Headache (Y,N) 2. Photophobia (Y,N)

3. Neck Stiffness (Y,N) 4. Kernigs (Y,N)

2.21 Cranial Nerve palsies (Y,N)

No of Cranial nerve(s):.....

2.22 Level Of Consciousness:

1. Alertness 2. Confusion 3. Drowsy 4. Coma

2.23 Motor system

1. Normal (Y,N) 2. Paraplegia (Y,N)

3. Hemiplegia (Y,N) 4. Weakness (Y,N)

2.24 Sensory 1. Normal (Y,N) 2. Impaired

2.25 **Laboratory Findings**

a) CSF: i. at start ii. at 6 weeks iii. at 12 weeks

1. Sugar: i.normal (Y,N) ii. low (Y,N) iii. High (Y,N)

2. Protein: i. normal (Y,N) ii. low (Y,N) iii. High (Y,N)

3. Culture Results

Polymorph i. absent ii. low iii. High

Lymphocytes i. absent ii. low iii. High

4. Electrolytes i. Cl ii Na

b) FBC

1. 1. Leukocytosis (Y,N) 2. Leukopenia (Y,N) 3. Anaemia (Y,N)

4. 4. Platelates (L,H) 5. ESR (L,H,N)

c) Malaria Parasite Positive (Y,N)

d) LFT i. at 6 weeks ii. at 12 weeks

i. Normal (Y,N) ii. High How high.....

e) U/Es i. Normal (Y,N) ii. High (Y,N)

5. CD_4 counts

2.26. Outcome at a. at 6 weeks b. at 12 weeks

Died at ..... weeks.

APPENDIX II

CONSENT FORM

I,.....

of.....

hereby consent to participation in the *cryptococcal* meningitis study the nature of which has been fully explained to me.

Date this:..... day of .....

Signed:..... .....

Witness.....