Occasional review

Cryptococcal meningitis

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SUMMARY Cryptococcosis is a systemic fungal disease and meningitis is the most serious complication. The purpose of this study is to define problems related to its diagnosis and treatment. This is a retrospective analysis of 25 patients admitted from January 1978 to December 1981. All patients had cryptococcal neoformans meningitis proven by culture of cerebrospinal fluid. One patient had a predisposing illness, being on immunosuppressant therapy after a renal transplant 2 years ago. A progressively severe headache of recent onset was the most striking presentation. Fever was frequently absent as a symptom. Cranial nerve palsies were commonly seen. Impairment of consciousness and areflexia signified a poor prognosis as all four patients who died early in the course of treatment were comatose and two of them were areflexic on admission. In newly suspected cases at least 3 separate lumbar punctures are recommended as initial smears or cultures may be negative. Cerebral CT scans were abnormal in 12 patients and those with cerebral oedema or hydrocephalus had a poorer prognosis. Combined amphotericin B and 5-fluorocytosine therapy was the treatment of choice. If there is no relapse 3 years after completion of treatment, patients are considered as cured. Positive smears may remain for years after completion of treatment and retreatment is only indicated if the cultures are positive. Twenty patients are alive today and none of them have relapsed. One patient had vasculitis of both anterior cerebral arteries as a result of cryptococcal meningitis.

Cryptococcosis is a systemic fungal infection and meningeal involvement is the most serious complication. As prognosis depends on early diagnosis and treatment, it is important to recognise this disease and be familiar with the clinical profile. The purpose of this paper is to define the problems related to the diagnosis and treatment as seen in our community.

Subjects and methods

Our study is a retrospective analysis of 25 consecutive patients with cryptococcal meningitis admitted to the Department of Neurology, Tan Tock Seng Hospital from January 1978 to December 1981. Twenty three patients were newly diagnosed and two patients were relapsed cases referred to the Department. All patients had cryptococcal meningitis as confirmed by culture from the cerebrospinal fluid.

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Results

(1) Population Study

The age of patients varied from 10 years to 67 years and the age distribution is shown in table 1. Forty per cent of cases occurred in the third decade of life. The sex and racial distribution is shown in table 2. There was no obvious sex or racial predominance.

(2) Clinical features

The clinical data of each patient is summarised in table 3. Symptoms and signs at time of presentation are shown in tables 4 and 5 respectively.

(a) *Headache.* The most common presentation was headache of recent onset. All except two patients (Nos 8, 25) had headache lasting one week to three months prior to being seen. The headaches characteristically increased in severity day by day.

(b) *Fever.* Only nine patients had low grade fever on presentation.

(c) *Neurological findings.* Ten patients had no neurological deficits at time of presentation. Cranial nerve palsies were most commonly seen. Eight patients had bilateral papilloedema and seven had

Table 1 Incidence of the disease in different age groups

Age (yr)	No of Cases
0-10	1
11-20	5
21-30	10
31-40	4
41-50	4
51-60	0
61-70	1

Table 2 Distribution of patients by sex & race

Race	No of Cases Male	Female
Chinese	10	9
Malay	2	3
Others	0	1

sixth cranial nerve palsies either unilateral or bilateral. Other cranial nerves were less commonly affected. Three patients were comatose on admission and all died within one week of hospitalization. Three patients were areflexic on admission and two of them were comatose.

(d) *Associated conditions.* All had no previous history of any serious illness except one patient who was on immunosuppressant therapy after a renal transplant 2 years previously.

(e) *Radiological findings.* The chest radiograph was abnormal in nine patients (Nos 3, 6, 8, 9, 12, 17, 20, 21, 24), with opacities in the upper and lower zones

in both lungs consistent with pulmonary cryptococcosis. Cerebral CT scans were done in all patients. Thirteen had normal scans at time of admission, six showed cerebral oedema either diffuse or focal, and five showed hydrocephalus. One had a normal scan initially and developed a non-communicating hydrocephalus 2 weeks later. One patient had cerebral angiography. The anterior cerebral arteries showed areas of irregular narrowing consistent with a vasculitis.

(f) *Laboratory data.* All patients had white blood cell counts of less than 10,000/mm³. The erythrocyte sedimentation rate was less than 20 mm per hour in all except two patients who had pulmonary tuberculosis as well. All had normal haemoglobin levels on presentation. The serum electrolytes were normal in conscious patients. Low serum sodium level (<110 meq/L) were present in all four patients who were drowsy or comatose on admission (Nos 3, 10, 17, 18).

(g) *Cerebrospinal fluid analysis.* The CSF data of all except one patient (no 18) can be seen in table 6. A normal cell count was seen in one patient (No 25). The average cell count was less than 200 cells/ml with one exception, who had a count of 1080 cells/ml. The cells showed a lymphocytic predominance. A low CSF glucose level was the rule. It was mostly less than 60 mg% and in two-thirds of the cases had a value less than 40 mg%. The protein concentration was normal in only five patients but the majority

Table 3 Background information on patients

Patient	Age (yr)	Sex	Race	Fever	Conscious state	Neurological deficits	Outcome
1	30	M	Ch	Absent	Drowsy	Bilateral papilloedema	Well
2	34	F	Ch	Present	Normal	No	Well
3	21	F	Ma	Present	Comatose	Bilateral VICN palsy, Areflexia	Died
4	11	F	Ch	Present	Normal	Bilateral VICN palsy, papilloedema	Well
5	13	F	Ma	Present	Drowsy	Bilateral papilloedema, Rt VII CN palsy, Rt hemiparesis	Well
6	48	F	Ch	Absent	Normal	No	Well
7	24	F	Ma	Absent	Drowsy	Bilateral VICN palsy, Rt hemiplegia	Rt hemiparesis
8	19	F	Ch	Absent	Normal	No	Died
9	24	M	Ch	Absent	Normal	Bilateral VICN palsy & papilloedema	Well
10	27	M	Ch	Present	Comatose	Bilateral optic atrophy III CN palsy	Died
11	67	F	Ch	Absent	Normal	Bilateral VICN palsy	Well
12	32	M	Ma	Present	Normal	Bilateral VICN palsy	Well
13	27	M	Ma	Present	Normal	No	Well
14	32	F	Ch	Absent	Normal	Bilateral VICN palsy, areflexia	Raised ICP
15	46	M	Ch	Absent	Normal	No	Well
16	45	F	Eu	Absent	Normal	Bilateral papilloedema	Raised ICP
17	19	F	Ch	Absent	Drowsy	Bilateral papilloedema	Died
18	46	M	Ch	Absent	Comatose	Areflexia	Died
19	25	M	Ch	Absent	Normal	No	Well
20	23	M	Ch	Absent	Normal	No	Well
21	22	F	Ch	Absent	Normal	Bilateral papilloedema and optic atrophy	Blind & Deaf
22	20	M	Ch	Present	Normal	No	Well
23	33	M	Ch	Present	Normal	No	Well
24	24	F	Ch	Absent	Normal	Bilateral papilloedema	Well
25	20	M	Ch	Absent	Normal	No	Well

Abbreviations: M = Male, F = Female, Ch = Chinese, Ma = Malay, Eu = Eurasian, CN = cranial nerve, ICP = Intracranial pressure, Rt = right.

Table 4 *Symptoms at time of presentation*

Symptoms	No of cases
Headache	23
Fever	9
Visual disturbance	9
Conscious state	7

Table 5 *Signs at time of presentation*

Signs	No of cases
Cranial nerve palsies	10
Papilloedema	8
Coma	4
Drowsiness	3
Areflexia	3
Long tract signs	2

ity had values of less than 2 g/l.

Nine patients had initial negative smears and cultures for cryptococcus. Two more lumbar punctures were done in these nine patients before a positive culture was obtained. The remaining 16 patients had positive smears and cultures at the first cerebrospinal fluid examination.

Measurement of cerebrospinal fluid cryptococcal antigen was done only in nine patients with initial negative smears. We found that those with positive cryptococcal antigen in the CSF had positive cultures eventually.

(3) Treatment Details

Twenty one patients had a combination of intravenous amphotericin B and oral 5-fluorocytosine. Two

patients had intravenous amphotericin B alone. The two relapsed cases had intrathecal amphotericin B and oral 5-fluorocytosine. Thirteen patients had oral garlic tablets in addition to the above. Amphotericin B was given intravenously at a dosage of 20 mg every other day until a total dose of at least 1 gm was reached. 5-fluorocytosine was given at a dosage of 150 mg/kg body weight per day in divided doses daily. Oral garlic tablets were given at 500 mg three times a day. The two relapsed cases had intrathecal amphotericin B. Patient No 25 had amphotericin B through the lumbar thecal space and patient No 24 through an Ommaya device. 0.5 mg amphotericin B was given every other day to a total dose of 15 mg unless complications arose.

The most common side effects of IV amphotericin B were hypokalaemia, mild renal impairment and fever. Lumbar arachnoiditis was the most common complication from intrathecal amphotericin B.

All patients were monitored with weekly full blood counts, urea and electrolytes and liver function tests. Of the five patients who developed hydrocephalus, all had ventricular shunts inserted. No complication arose from shunt insertion.

Four patients (Nos 8, 9, 20, 24) had pulmonary lobectomies for removal of their lung lesions. All showed pulmonary cryptococcosis on histology.

(4) Follow-up details

Twenty patients are alive today and 18 of them have returned to their original jobs. One has bilateral deafness and blindness and the other has a dense right hemiplegia. Two other patients although well,

Table 6 *The cerebrospinal fluid of patients before treatment*

Patient	Cells	Glucose	Protein g/l	Globulin	Chloride	Smear
1	Unsuitable	28	0.6	+	603	+
2	123	44	0.4	—	729	+
3	Unsuitable	20	0.3	—	655	+
4	280	53	0.8	+	673	+
5	60	24	0.5	Trace	726	+
6	Unsuitable	20	1.0	+	725	+
7	8	10	0.4	+	608	+
8	120	36	0.5	+	638	+
9	170	35	2.0	+	696	+
10	14	30	0.9	+	585	+
11	120	62	0.8	+	655	+
12	82	37	1.0	+	708	—
13	125	34	0.8	+	690	—
14	Unsuitable	60	0.2	—	731	—
15	107	15	2.8	+	705	+
16	6	67	0.3	—	679	—
17	Unsuitable	46	0.3	—	714	—
18	—	—	—	—	—	—
19	190	20	1.0	+	667	+
20	44	54	0.2	—	700	+
21	Unsuitable	10	0.6	+	661	+
22	150	20	0.7	+	673	—
23	1082	112	1.0	+	70	—
24	18	43	2.4	+	760	+
25	4	26	0.4	—	673	+

have persistently raised intracranial pressure with no evidence of relapse even at 3 years after completion of treatment. Both these patients need intermittent tapping of CSF to reduce intracranial pressure. However they are able to carry on with their jobs normally. Five patients died, four within a week of commencing treatment. All four were comatose at the onset of illness. The last patient had unexplained sudden death 4 months after successful completion of treatment. No necropsy was done in this patient.

Discussion

Cryptococcosis is an infectious disease in both man and animals. In man it results from inhalation of the encapsulated yeast-like fungus, *cryptococcus neoformans*. This organism is found abundantly in avian excreta and soil. The lungs are the primary site of entry. Following this the organism either remains in the lungs or disseminates to any other part of the body. Overt CNS infection is invariably fatal if left untreated.¹ However there have been reports of death from pulmonary cryptococcosis *per se*.^{2,3}

The wide age range of 10 to 67 years in our study and the maximum incidence in the third decade compares well with other series. There was neither racial nor sex predominance. No occupational risk group could be identified.

Cryptococcosis has been described as an opportunistic pathogen in immune compromised hosts.⁴⁻⁶ It is seen in lymphoreticular malignancies, systemic lupus erythematosus, diabetes mellitus and those on prolonged steroid therapy or other immunosuppressive agents. However it has been reported in healthy subjects as well.⁷⁻⁹ Strikingly only one of the patients in this study had a predisposing factor. She was on steroid and immunosuppressant therapy after a renal transplant 2 years prior to the onset of meningitis. The rest of the patients were apparently healthy.

Cerebral cryptococcosis can present in various forms, which, in order of frequency, include chronic meningitis, encephalitis, space-occupying lesion or mental change.^{10,11}

A short history of headache (less than 3/12) was the most striking symptom. The duration of headache was not associated with the severity of disease. Fever was frequently absent as a symptom and sign. Only nine patients had a fever (which was low grade), on presentation. Cranial nerves palsies were commonly seen. The sixth cranial nerve palsy and papilloedema was frequently found as a result of raised intracranial pressure. However, third, seventh and eighth cranial nerve palsies were also seen and were possibly the result of basal arachnoiditis. The combination of a severe headache and papilloedema

may mislead one to diagnose a posterior fossa tumour and cause delay in doing a lumbar puncture. This presentation was in fact very common in our patients. We would advocate an early CSF examination after cerebral CT scan show no space-occupying lesion. However, cerebral cryptococcosis can also present as a mass lesion with or without hydrocephalus.^{12,13} Examination of ventricular fluid or examination of the mass during craniotomy would lead to the diagnosis. This presentation was not seen in this series.

Complete areflexia was seen in three patients and two patients died within one week of treatment. The areflexia could have resulted from a severe generalised spinal arachnoiditis. The initial lumbar fluid analysis in one of these patients revealed gelatinous material which is characteristic of an acute early infection.¹¹ All four patients with impaired consciousness at onset died. Overt psychiatric changes were not seen at presentation.

A diagnosis of cryptococcal meningitis can only be confirmed by CSF culture. The classical method of detecting cryptococci is to add a drop of Indian ink to a drop of spinal fluid and then examine it under the microscope.¹⁴ The only encapsulated yeast that invades the CNS is the *cryptococcus*. Therefore the presence of this yeast form in CSF smear of patient without prior treatment is adequate for diagnosis. Although smears and cultures were negative on initial examination in nine patients, performing lumbar punctures up to three times yielded positive cultures eventually. We therefore recommend that in the face of a negative initial CSF examination in a suspect case, further lumbar punctures (at least three in all) should be performed. After treatment positive smears may still persist for up to 2 years but cultures from CSF should be negative. Based on experimental work,^{15,16} it is recommended that a minimum of 5 ml of CSF be cultured when a CNS mycoses is suspected.

Measurement of cryptococcal antigen in the serum of CSF is a useful adjunct to diagnosis. However there are reports of false positives^{17,18} and negatives.¹⁹ In the CSF profile the protein content was usually raised but less than 2 g/l. The cell count though variable, was usually less than 200 cells/mm³. They were predominantly lymphocytes. We found no correlation between severity of disease with degree of pleocytosis, glucose level and protein content. This has been noted before.²⁰

The serum electrolytes and erythrocyte sedimentation rate were measured in all patients. Despite evidence of constitutional involvement with fever, the erythrocyte sedimentation rate remained normal except in two patients who had concomitant pulmonary tuberculosis. The syndrome of inappropriate

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antidiuretic hormone secretion is commonly seen in various neurological disorders, and we had four patients with low serum sodium (less than 110 mg/R). We found the combination of low serum sodium with impaired consciousness to be ominous as all these four died. We believe they had the syndrome of inappropriate antidiuretic hormone secretion although biochemical confirmatory tests were not done.

All patients had cerebral CT scans done, the CT scan abnormalities include cerebral oedema, hydrocephalus and mass lesions.²¹ None of our patients had mass lesions. Out of the six patients with cerebral oedema, three patients died early in the course of treatment. Two patients have problems of persistent raised intracranial pressure even 3 years after completion of treatment. Only one patient has remained well. Five patients had hydrocephalus on CT scans. Only one died in the course of illness. Another is blind and deaf. Of the remaining three, two are well with no complications and one has a mild residual right hemiparesis. From this small selection of patients with CT scan abnormalities we infer that cerebral oedema and hydrocephalus can be associated with greater morbidity and mortality.

Cerebral angiography was done for patient no 5. She had a persistent low density area in the left frontal lobe, corresponding to area of infarction. Both the anterior cerebral arteries showed areas of irregular narrowing suggesting the presence of a vasculitis. Hence neurological damage seen in the cryptococcal meningitis could be due to the direct invasion of the brain by the fungus itself or as a result of vasculitis. This has not been reported before.

For treatment, intravenous amphotericin B and oral 5-fluorocytosine is the combination of choice.²²⁻²⁶ For severe infections or relapsed cases, amphotericin B can be given through the subarachnoid space.²⁷ Amphotericin B is usually poorly tolerated in high doses and we find that our local patients can only tolerate 20 mg/day without having any renal complication. Other studies advocate intravenous amphotericin B at 1 mg/kg body weight daily up to a total dose of 1-3 g. We have used intravenous amphotericin B at a lower dosage, 20 mg every other day up to at least 1 g total dose without loss of efficacy. At this dosage complications were minimal. Mild renal impairment and hypokalaemia were most commonly seen and they were easily reversed with temporary stoppage of the drug. For intrathecal amphotericin B the recommended dose is a total of 15 mg.²⁸

5-fluorocytosine is a synthetic antifungal agent. When used alone for cryptococcal meningitis drug resistance develops rapidly.²⁹ It is best used in combination with amphotericin B. The dosage used in

our patients was 150 mg/kg body weight in divided doses. Although it is not nephrotoxic, dosage must be reduced in patients with renal disorders as this drug is excreted by the kidneys. No serious complications arose from 5-fluorocytosine. As all patients responded to amphotericin B and 5-fluorocytosine, other antifungal agents was not used in this study.

Miconazole, an imidazole derivative has been used in patients with renal impairment as the drug is not nephrotoxic. However for success in treatment simultaneous intravenous and intrathecal therapy is recommended.³⁰ Miconazole and amphotericin B should not be given together because antagonistic effects between both drugs has been demonstrated both *in vivo* and *in vitro*.³¹

Ketoconazole, another new antifungal agent is useful in non-CNS cryptococcosis. One patient (No 24) had ketoconazole for a pulmonary lesion with concomitant intrathecal amphotericin B and 5-fluorocytosine. There are reports of treatment failure with ketoconazole in cryptococcal meningitis,³² as the drug does not cross the blood-brain barrier well.

Garlic has been reported to have a fungistatic action and improves the patient's immune status.³³ Successful treatment of cryptococcal meningitis using garlic derivatives has been reported. Thirteen patients were given garlic tablets in addition to amphotericin B and 5-fluorocytosine. As cryptococcal meningitis is a life threatening infection, garlic should not be used alone until further reports become available.

On completion of treatment all patients were followed up 3 monthly for the first year and 6 monthly thereafter with lumbar punctures done on each visit. All were followed up for a minimum period of 3 years before considered cured. Today there are 20 survivors and four have residual disabilities. This is an improvement in mortality rate compared to other studies.

In conclusion, this disease can occur in healthy patients especially in the Orient, as compared with the studies from the west. A progressively severe headache of recent onset is a striking symptom and together with papilloedema or cranial nerve palsies, a diagnosis of cryptococcal meningitis must be excluded. A minimum of three separate lumbar punctures should be done in a suspect patient, if the initial CSF is negative. Impairment of conscious level associated with areflexia and low serum sodium is a fatal prognostic sign. The CSF profile bears no correlation with severity of illness and ultimate prognosis. Cerebral oedema and hydrocephalus seen on CT scans were related to a greater morbidity or mortality.

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