Cryptococcal meningitis in HIV infected patients – a retrospective study of S.Marcos Hospital experience from 1998 to 2004

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Abstract

Cryptococcosis is a fungal infection caused by Cryptococcus neoformans. This article describes, retrospectively, the number of HIV patients at S. Marcos Hospital diagnosed with cryptococcal meningitis, from January 1998 to July 2004. During this 66 month period 18 cases have been identified. In our series there was no correlation between the stage of the HIV infection and the clinical manifestations at the time of admission. Given that no association was found between the initial clinical manifestations and opening pressure in the initial lumbar puncture, the former may not be taken as a reliable indicator of the need to decrease the intracranial pressure. Our work re-emphasizes the importance of evaluating the opening pressure, as a means to diagnose intracranial hypertension. The drainage of liquor, eventually backed by appropriate neurosurgical techniques, is an adequate alternative method to alleviate intracranial hypertension, when strong evidence supporting the use of medication for that purpose is scarce. The reduction of mortality and morbidity relies on an aggressive approach, which combines the use of anti-fungal therapy with external drainage, or even peritoneal shunting.

Key words: meningitis, Cryptococcus, HIV infection, intracranial hypertension.

Introduction

Cryptococcosis is a systemic infection caused by an encapsulated fungus, Cryptococcus neoformans; it is thought the primary infection occurs after inhalation, and the hematogenous dissemination leads to reach the meningeum depending on the patient's immune condition.[1] Cryptococcal meningitis is an uncommon disease in immunocompetent patients (before the experience with the Human Immunodeficiency Virus infected patients – the experience was lower than 100 patients/ year in the USA[2]).

At present, it is known this pathology is the most common CNS fungal infection, while opportunistic, in HIV infected patients; before introducing the anti-retroviral therapy with protease inhibitors[2] reaching 5 to 10% of these patients, often as defining condition. In over 50% of cases it is associated with an increase on intracranial pressure (defined as >200 mmH_2O [2]).

In spite of being described a reduced incidence rate since the introduction of anti-retroviral therapy, in our environment, we have seen, on the contrary an increase in the number of the cases per year, with special emphasis of diagnosis on new cases of HIV infection.

In this work, there was a retrospective assessment on the number of cases of cryptococcal meningitis admitted at S. Marcos Hospital (HSM), from the 1st January 1998 to the 30th June 2004. It was included a patient seen initially in another hospital and transferred, after diagnosis, to the HSM, to keep his treatment.

Patients and methods

The clinical files of 18 patients with a Cryptococcal meningitis diagnosis and admitted to our hospital, for a period of 66 months from the 1st January 1998 to the 30th June 2004, aged 15 years old or more, were evaluated.

All were admitted in the Internal Medicine and/ or Neurology services, with common observations by both specialties.

The following variable were assessed: the population characteristics referring to gender, age, cryptococcal infection date, risk factor for HIV infection, the HIV infection stage (T lymphocytes CD4 count

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by flow cytometry, viral load though the b-DNA technique), the situations it became a defining disease, symptoms (vomiting, headache, diplopia) and signs (fever, nape of neck stiffness, focal neurologic signs, cranial nerves paresis), progression time; CSF features (biochemistry, cytology); brain CAT Scan outcome in the cases it was made; the treatment made and the time elapsed up to its beginning, the intercurrence presented, the final outcome (defined as improved, deceased, relapse or recurrence).

The Cryptococcal meningitis diagnosis was made after a culture to isolate the agent and/or a positive identification in the direct exam with Indian ink or a title of Cryptococcal antigen in the cerebrospinal fluid (CSF). In the cases of evaluating the opening pressure in the CSF, values not higher than 190 mmH_2O were deemed as normal.[2]

We define recurrence as a new episode of meningitis after a 3 week period or more from the treatment ending and recurrence, if the gap from one episode to the other was less than 3 weeks.

The statistic assessment of data was made using SPSS 12.0 software for Windows, resorting to several categoric variables in the Chi square and continuous at Student's t-test . The significant level considered was 0.05.

Results

During the period of 66 months referred, 18 cases of cryptococcal meningitis were diagnosed with the following yearly distribution (*Fig 1)* and the following characteristics:

Population

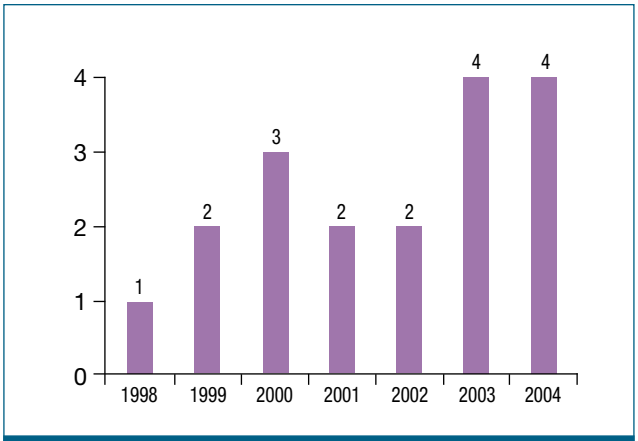
The patients average age was 38,0 years old, being 16 (88.8%) of male gender. All presented HIV infection, known or diagnosed after admission.

In 44% of the total, it was made the first manifestation of HIV infection and it was defined as Acquired Immunodeficiency Syndrome (AIDS), in most affected patients, 11 (61.0%).

In 6 patients there was a previous history of opportunistic infection (ganglionary tuberculosis, pulmonary or disseminated, cerebral toxoplasmosis and esophagic candidiasis).

The risk behavior for HIV infection was the heterosexual in 10 patients (56%) and drug addiction in 8 (44%).

Regarding the immune stage, 50% presented at the date of the diagnosis a T- lymphocyte CD4 count lower than 50; 6 patients (33,3%) from 50 to 200 and only 3 (16,7%) between 200 and 350; none had values above 350.



Yearly distribution of the cryptococcal meningitis in HIV infected patients.

FIG. 1

Viral loads (bDNA) were higher than 55,000 in 4 patients (22.2%); from 10,000 to 55,000 in 5 (27.8%); from 50 to 10,000 in 1 and lower than 50 in 3 (16.6%). The latter are not known in 5 patients.

Symptoms

In 7 patients, the symptoms had evolved for weeks (38.9%), 6 evolving in days (33.3%) and 4 with an evolution lower than 24h (22.2%).

The main symptoms shown in admission were headache (in 13 cases, 9 with simultaneous CIH), vomiting (in 7 cases, 5 with CIH), diplopia (3, one with CIH) and dysphagia (one with associated CIH).

The most frequent clinical signs presented on admission were fever (in 11 patients, 7 with simultaneous CIH), nape of neck stiffness (8, 5 with CIH), papillary edema (3, all with CIH), focal neurological signs (2, one with CIH), VI pair paresis (2 cases, but only one with documented CIH) and confusion or lethargy (3 cases, one with CIH).

In 4 of these patients, at the moment of the first observation, was possible to observe oral candidiasis, in 2 compatible lesions with Molluscum contagiosum and 1 in open exacerbation of the psoriasis condition.

With exception of 4 patients, all had initially a Glasgow Coma Score (ECG) of 15/15. In 2, that was

14/15 (both relapsed after treatment of the initial episode) and two of 13/15.

Imagiology exams

All patients were subject to a CAT scan on admission. In 15 (83.3%) it was described as "normal".

In the three remaining the changes meant toxoplasmosis sequelae lesions.

Only in two patients, this exam was repeated after the first 72 hours, always because a new deficit emerges or there is a change in the state of awareness regarding the admission.

Cerebrospinal fluid

In the first observation, at the Emergency Service, only the pressure in the lumbar puncture pressure was evaluated in 10 patients (55.5%), and it was not normal in any of them. In *Fig 2* it is revealed the number of patients with the found values (referred as Opening Pressure) and its relation with the number of recurrent cases (referred as R); the opening pressures are values in mmH_2O.

CSF cytology and biochemistry

We do not know the initial changes in the transferred patient. In 6 patients, CSF changes were compatible with non-inflammatory CSF (≤5 cells, normal glychorrhachia and proteinorrhachia); 2 of these patients died, one after recurrence.

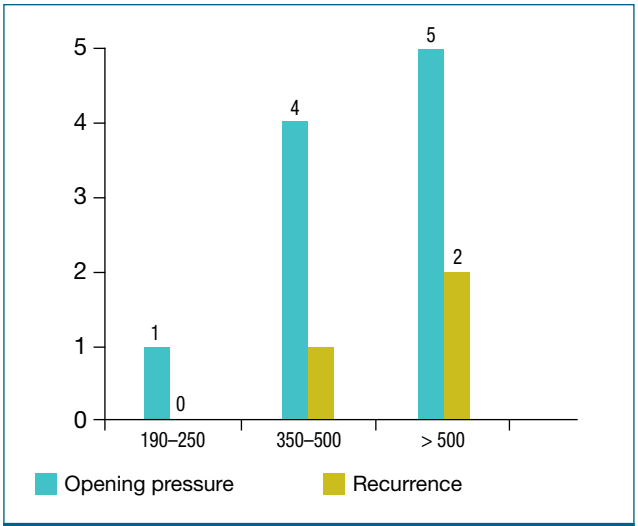
The remaining 11 had > 5 cells (one with 930 cells in the first Lumbar Puncture) with a predominance of lymphocytes, hypoglorrhachia (sometimes marked) and an increase on the protein value (> 45 mg/dL).

From these, 3 died.

The infection diagnosis was made with a cultural isolation from the agent in CSF (in 15 patients), by the title of Cryptococcal antigens (positive in 12 patients) and/or by the visualization in the direct exam with Indian ink (positive in 8 patients all confirmed with a culture exam).

In 9 cases (50%) the lumbar puncture (LP) was repeated (in less than a week, for the symptomatic relief or due to a worsening of the neurologic conditions; 2 weeks after the treatment onset). In 6 cases there was a LP repetition (three or four times – to relief intracranial pressure).

From the patients with repeated LP, only one died; in most there was an evaluation when admitted, of the opening pressure, which was high. Only in one case of repeating the exam on the 2nd week that was not evaluated.



Opening pressure values relating with recurrence

FIG. 2

Treatment

The time elapsed until the beginning of the specific treatment was the equivalent to the diagnosis.

It was below 24 hours in 11 patients (61.1%), although in this group there is the death of a patient with a subsequent relapse and 5 recurrences.

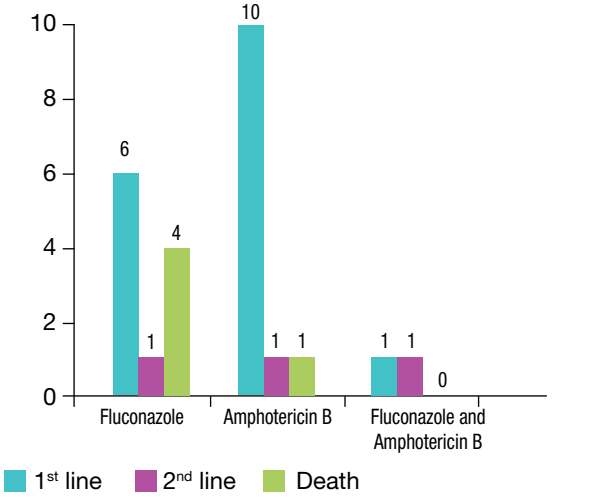
In 7 patients with treatment started after 24 hours, one started after 3 weeks, one after one week, 3 after 4 days, one after 48 hours and one at 25 hours. In this group 3 patients died (42.8%), but none has relapsed.

In 6 cases (35.3%) therapy was started with fluconazole, 4 of them died (1 after recurrence). In one of the recurrences, a patient medicated initially with amphotericin B, had a successful sterilization of the CSF with a therapy change for fluconazole.

In 11 patients (61.1%) the beginning of the treatment was with amphotericin B; 1 patient started it as second line therapy after a clinical worsening with fluconazole. In this group a fatal case was reported.

In one case, starting treatment with amphotericin B and fluconazole concomitantly, added to another patient that had this therapy scheme as 2nd line (*Fig 3*).

Only 6 patients (33.3%) started corticoids (dexamethasone), 5 in a period less than 24 h. This group includes 3 fatal cases.



Antifungal treatment made.

FIG. 3

Manitol was used in a recurrence, acetazolamide was never used.

Another therapy, unique or concomitantly, was started in 5 patients: 1 patient with cefotaxime, 1 patient with tuberculostatic and 2 with tuberculostatic and cefotaxime.

These drugs were suspended after the diagnosis of Cryptococcal meningitis, one of the cases for 3 weeks, time to isolate the agent in culture of the patient with unknown HIV infection.

A patient was medicated with an association of cefotaxime and vancomycin, by concomitant bacterial meningitis (see complications). In one of the relapses, construed initially as bacterial meningitis, the patient was medicated with ceftriaxone for 2 weeks.

Complications

There was a worsening of the conscious state with a change on the Glasgow coma score (ECG) in 2 patients – from 5 to 13/15 on the 3rd day and to 8/15 on the 4th day. None of them had yet started specific therapy. On admission it was not evaluated intracranial pressure. Both of them died.

The coma patient has evolved to a condition compatible with right pneumonia, during admission.

In a patient with pretreatment opening pressure above 500, even with an early start with amphotericin B, a convulsive crisis was seen on the 2nd day and death occurred on the 4th day.

In 2 cases, on the 2nd week of amphotericin B (liposomal) therapy, it was seen a development of non-oliguric acute renal failure, with a full recovery after the drug withdrawal.

On the 18th admission day, a patient with a story of three previous lumbar punctures, changes in the CSF were seen as well as a clinical deterioration, compatible with bacterial meningitis –, the agent was not isolated but it was seen a clinical resolution after an association of cefotaxime and vancomycin to the therapy scheme.

A patient evolved with uveitis during admission; another shown an unbalance of a chronic liver disease (liver cirrhosis in a context of chronic C hepatitis diagnosed during admission) and medullary aplasia, and death occurred due to an unbalance liver cirrhosis 6 months after a meningitis episode.

Final

In 9 cases (50%) it was seen an improvement with initial treatment or a 2nd line. There were 5 deaths (29.4%) directly related with a meningitis episode, respectively on the 4th, 6th, 8th and 9th days of admission and to the 2nd recurrence six months after the initial diagnosis. Only 2 of these patients had a intracranial pressure evaluation on admission (this is higher than 500 mmH_2O).

We assisted to recurrence and relapses in 5 patients, 1 has died subsequently and was included in the previous group.

In 2, intracranial pressures were persistently high, even after CSF sterilization – patient 5, deceased and patient 1 with improvement after placement of lumboperitoneal shunt.

Discussion

Cryptococcal meningitis has been traditionally considered a chronic granulomatous meningitis,[2] lymphocytic and diffuse with inflammation foci in the meninges and cerebral foci lesions.

When associated to AIDS this meningitis is less presumed as a lymphocytic choriomeningitis and more as a massive fungal *infestation* almost without an inflammatory response. It is thought that Cryptococcus cause a mechanical obstruction to the CSF flow through the arachnoid villi; apart of that, cryptococcal capsular polysccharide aggregates can accumulate in the villi and subarachnoidal spaces, leaving as the CSF main draining route the lymphatic channel and

interfering with the exit of the interstitial fluid for those spaces, leading to cerebral parenchyma edema,[3] also present in this disease.

Different from the immunocompetent, such patients seldom evolve to hydrochepalia.

There are studies[2] in which the tomography changes were only evident in 35% of patients (it can be read cerebral atrophy, foci lesions, white matter lesions and meningeal enhancement), and in none of them was detected hydrocephalia. As in our sample, no radiology change was consistently predictive of an intracranial pressure increase.[4] The presence of cryptococcomas as irregular marginal lesions, in most cases confluent and located in the basal ganglia, with a minimum enhancement after contrast is rare. It seems to us excessive the usual description of a normal exam occurring in 82% of cases, in our sample.

A high percentage of patients had an initial diagnosis of HIV infection – 43% – what raises the awareness for the need of a high level of suspicion while approaching a patient with headache and fever. There is, however, other series[1,5] in which it was the first manifestation of AIDS in 40% to 45% of cases.

The disease stage was not correlated with the clinic on admission, in our series. In our group, it was statistically significant the relation between the presence of fever and the final outcome (p=0.018), and most patients had a favorable evolution and none of the deceased had shown it when entering. As in other series, fever and headache are important symptoms, reason why in patients with advanced HIV infection are key signs to the diagnosis, specially associated with vomiting, nape of neck stiffness or confusion.

In recurrence and relapses, headaches were the most frequent symptoms, in spite of, as it is recognized, those can manifest themselves as only occasional fever, being the incidence of headaches and nape of neck stiffness less frequent than in the initial episode. It was found a statistically significant association between headache as initial clinical manifestation and the presence of counting T lymphocytes CD4 < than 50 (p=0.012). It was also the relation between the presence of papillary edema at the beginning the subsequent recurrence (p=0.009).

The VI pair paresis was present in 2 patients, one with verified intracranial pressure, another deceased. The association between VI pair (p=0.019) the clinical manifestation associated to death (both patients died) it was revealed with statistic significance (p=0.019).

The most sensitive test for this pathology seems to be the cryptococcal agent in the CSF.[4] To bear in mind that low titles can be kept in the induction stage, in spite of a positive outcome. The serial presence of such antigen can also reveal itself useful as a positive predictive factor (in the case of patients with HIV infection and cryptococcal meningitis is of 92%) in patients where lumbar puncture is not indicated.[1] Not always, is found in the CSF pleocytosis with characteristic hypoglycorrhachia, although it can be normal in around half of the immunodepressed patients.

In some studies (Zerpa and al J. Clin. Microbiology,1990), cultures are positive in over 85% and the direct exam with Indian ink in 75%.

With the advent of antifungal therapy[6] survival rates are around 60-70%; before 1950 it was almost always a fatal disease. With 2 weeks of treatment with amphotericin B and flucitosine it is achieved the sterilization of CSF in 60 to 90%.[20] In spite of that, there are recorded mortality rates in patients with cryptococcal meningitis and HIV infection in around 25%. We had 22% mortality, a little higher than in other series,[3,8,9] mainly in the initial stage where intracranial hypertension was initially diagnosed, although not adopting immediately any step to pressure control.

The time until the treatment was not related with a worst prognosis (p-0.051), as well as the type of initial treatment. However, it should be highlighted that such fact can be due to the small size of the sample, and it is worth noticing that in the group it was started fluconozole as initial treatment, four patients died although only one patient died in the amphotericin group, what is in accordance with other series in the literature.

The AIDS Clinical Trial Group[3] has identified only three predictive factors of high mortality during a anti-mycosis treatment: cognitive changes to presentation, cryptococcal antigen title in the CSF higher than >1:1024 and a lower value of 20/ul leukocytes in the CSF.[1,10]

It was also found[2,3] an association between a high intracranial pressure and mortality in the first week. Both in immunocompetent patients as in co-infected patients with HIV infection, intracranial hypertension (defined as opening pressure > 250 mmH_2O in patients in lateral decubitus) emerges in almost half of the cases.[6]

As expected, most of our symptomatic patients showed high opening pressures.

The repetition of lumbar puncture was associated (p=0.033) to a better prognosis; curiously, the posterior repetition with > 2 LP did not have the same value as a statistical association (perhaps due to the reduced number subject to these, 7 in total).

The relation between a high opening pressure and a lower number of T lymphocytes CD4 was also statistically relevant (p = 0.040).

Curiously, it was not found an association between the initial clinical manifestations and the opening pressure, what makes impossible to trust those as indicators of the need to evaluate intracranial pressure. It is also possible that the reduced number of cases in that such endpoint was evaluated makes impossible to found a relation with statistic power. In fact, it was relevant the absence of evaluation in 43% of the cases.

Possibly as important the anti-fungal therapy in the treatment of cryptococcal meningitis is the aggressive control of this intracranial hypertension.[11,12,18] In spite of hypertension being often associated to clinical symptoms and signs as papilledema, hypoacusia, pathologic reflex and delay in the mycologic clearance in the CSF at 2 week,[2] as noted in our series and mentioned in others,[13] can evolve in a silent mode, what makes necessary to assume as usual the evaluation of the opening pressure while approaching such patients. In such cases, the quick control of these pressures through the drainage of liquor through sequential lumbar punctures, or even being considered the early implantation of peritoneal shunts, it seems to assume a prognosis importance. Often, there is the fear that frequent lumbar punctures and with high volume drainage in patients with intracranial hypertension lead to cerebral herniation. Antinori [14] mentions the existence of 2 cases of cryptococcal meningitis with loss of knowledge and death after lumber puncture; in the autopsy, the cerebral herniation was considered the cause of death. However, other explanation can justify such outcome, i.e., the fact that liquor drainage was inadequate to the hypertension degree keeping a high pressure which would justify, on its own, the herniation.

The medical steps, namely the use of manitol, acetazolamide or corticoids (in this case, except cases of intracranial hypertension, in the context of immune reconstitution syndrome), have not been shown effective in the control of cerebral pressure.[3,11] Graybill and al. mention that even corticosteroids are associated with a mycologic failure and a clinical e premature death.[2] But other authors[11] advocate that, probably the higher severity of patients who receive corticotherapy represent a deviation to the conclusion due to the analysis of the results, although it is not well defined the effective value of corticotherapy in these patients. In relation to acetazolamide, already in 2001[15] an essay with 22 patients with cryptococcal meningitis and opening pressures above 200 mmH2O was prematurely stopped due to the side effects of drugs without improving the survival rates relating to placebo.

Therefore, it is advocated[3,11] that in patients with a pré-treatment opening lower than 200 mmH_2O, the second lumbar puncture should be made at 2 weeks, to exclude hypertension development and to evaluate the culture status. In other patients with baseline hypertension, it is recommended, immediately the reduction to half of the opening pressure, performing all necessary punctures to keep it normal; after this value returning to normal such procedure can be stopped. It has been considered, ever more, the peritoneal shunt (ventricle or lumboperitoneal) in patients where repeated punctures have failed in the desired control or when the neurologic deficits are persistent or progressive (keeping hypertension).[3,2] The shunt secondary infection, by cryptococcos in patients under antifungal therapy is rare. It is advocated that, in spite of the immunosupression and a persistent infection of CSF, in the cases of cryptococcal meningitis, the shunt must be a solution to the relief of sustainable high pressure, in spite of the frequent external drainages.[16] It is not associated to an infection dissemination, does not avoid the mycologic cure and seldom is subject to later reviews.[17,18] In the liquor assessment and before conclude the infection persistence, it is necessary to remember that pleocytosis can persist up to 6 to12 months after a anti-fungal treatment with success.

Other studies, in 2002,[13,6] have already referred the neurologic deficits that do not respond to the pharmacology treatment were solved with a ventriculoperitoneal shunt, even in the absence of hydrocephalia.[19] In patients with this pathology and with baseline papilledema with a reduced visual acuity[4] that, immediately, were subject to aggressive steps to intracranial pressure (including peritoneal shunt),

were recorded the regression of visual deficits.

Facing the values found as opening pressure and their implications in the subsequent control of the opening pressure seems important to emphasize the need of this procedure, as in this small series, its relief had a direct relation with the number of recurrences.

Conclusion

We presented our experience in the last 66 months in the treatment of patients with cryptococcal meningitis. This experience emphasizes the importance of evaluating the opening pressure as means to diagnose the presence of intracranial pressure, common characteristic in this type of meningitis.

It has ever more emphasized the importance of evaluating the opening pressure facing the prognosis value that this seems to assume in this entity.[2,13]

In our sample, in all patients it was evaluated the baseline pressure (55.5%), and without any relation with clinical symptoms and signs that could alert to this fact. In the absence of any safe evidence to use the pharmacology steps to relief the intracranial pressure, the liquor drainage seems to be an effective approach to this objective, resorting eventually to neurosurgical techniques. AIDS patients and cryptococcal meningitis with visual deficit or ocular paralysis with high opening pressures must be early guided to the placement of shunts. The manometric evaluation of the liquor pressure it is assumed as of vital importance in the approach of patients with this pathology, enable to diagnose immediately the need to an aggressive approach to intracranial hypertension with the consequences already mentioned in reducing morbidity and mortality associated to this pathology.[3,6]

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