Clinical Manifestations of Cryptococcal Meningitis in HIV Negative Patients-A Case Study

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Abstract

Cryptococcal Meningitis (CM) is a central nervous system infection caused by a fungus. A large majority of cases are caused by Cryptococcus neoformans var. neoformans. The fungus C. neoformans is found in soil that contains bird droppings, particularly pigeon excreta, all over the world. Cryptococcusneoformans var. gatti, on the other hand, is found primarily in tropical and subtropical regions trees, most commonly eucalyptus trees. It grows in the debris around the trees' bases. Cryptococcal meningitis usually occurs in people who have a compromised immune system and is a rare occurrence in someone who has a normal immune system. Of the two fungi, Cryptococcalgattii is the one more likely to infect someone with a normal immune system.The incidence of infections caused by C.neoformans has risen markedly over the past 20 years as a result of the HIV/AIDS epidemic and increasing use of immunosuppressive therapies. Cryptococcal meningitis is a common opportunistic infection and an AIDS-defining illness in patients with late-stage HIV infection, particularly in Southeast Asia and Southern and East Africa. It is widely considered as the most common life-threatening AIDS related fungal infection. Cryptococcal meningitis has been estimated at about 70 to 90% worldwide in AIDS patients with mortalities of between 50% to 70% in Sub-Saharan Africa. [2,3,4] Mortality from HIV-associated cryptococcal meningitis remains high (13–33%), even in developed countries, because of the inadequacy of current antifungal drugs and combinations, and the complication of raised intracranial pressure.[2,7,8]In the cases presented, the findings were so non-specific that the diagnosis was highly dependent on the CSF findings. Based on the characteristics of the presenting signs and symptoms, Cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis, since clinical features are not specific.

Key Words *Cryptococcus Neoformans var. Neoformans, Cryptococcus Neoformans var. gatti, Immune system, immunocompetent, immune suppression, AIDS defining, Meningitis, Meningism, Lumber Puncture, Cerebral Spinal Fluid, Central Nervous System, Disseminated Cryptococcosis, Fungal Infection, Fluconazole.*

1. Introduction

Cryptococcal Meningitis (CM) is a central nervous system infection caused by a fungus. A large majority of cases are caused by Cryptococcus neoformans var. neoformans. This fungus is found in soil all over the world. It is usually found in soil that contains bird droppings, particularly pigeon excreta. Cryptococcusneoformans var.gattii, on the other hand, is found primarily in tropical and subtropical regions trees, most commonly eucalyptus trees. It grows in the debris around the trees' bases. Cryptococcal meningitis usually occurs in people who have a compromised immune system and is a rare occurrence in someone who has a normal immune system. Of the two fungi that can cause the condition, cryptococcalgattii is the one more likely to infect someone with a normal immune system. [1, 2, 3]

The incidence of infections caused by the encapsulated yeast Cryptococcus neoformans has risen markedly over the past 20 years as a result of the HIV/AIDS epidemic and increasing use of immunosuppressive therapies. Cryptococcal meningitis is a common opportunistic infection and AIDS-defining illness in patients with late-stage HIV infection, particularly in Southeast Asia and Southern and East Africa. [2, 3, 4] It is widely considered as the most

common life-threatening AIDS related fungal infection. Worldwide, 36.9 million people are infected with HIV, out of which 25.8 million (70%) live in Sub-Saharan Africa.[UNAIDS Fact Sheet 2015]In Zambia, 15% of women and 11% of men (average of 13% of adults) age 15-49 are infected with HIV.The number is reflective of an 87% counselling and testing rate in the population.[5]Cryptococcal meningitis has been estimated at about 70 to 90% worldwide in AIDS patients with mortalities of between 50% to 70% in Sub-Saharan Africa.[,6,7,8] In parts of sub-Saharan Africa with the highest HIV prevalence, cryptococcal meningitis is now the leading cause of community-acquired meningitis, ahead of Streptococcus pneumoniae and Neisseria meningitides. Mortality from HIV-associated cryptococcalmeningitis remains high (13–33%), even in developed countries, because of the inadequacy of current antifungal drugs and combinations, and the complication of raised intracranial pressure. [2, 7, 8]

Studies from South America have reported both species in the decaying heartwood of a number of trees.10The presence of a laccase enzyme in both species that could be involved in the breakdown of lignin and the fact that C.neoformans and C.gattii are closely related to other wood-rotting fungi might be a significantecological find.13 Serological studies suggest that most individuals are exposed to the organism, starting after the first 2 years of life.14 However, the precise circumstances and frequency of exposure, like the ecology of the organism, are still not completely understood. With this in mind, for reasons unknown, an unprecedented outbreak of C.gattii infections has been occurring since 1999 in over 50 immunocompetent patients and animals as diverse as dogs, cats, llamas and porpoises on Vancouver Island, Canada. 1999 (218 cases reported during 1999 – 2007) and in the US Pacific Northwest since 2004 (96 cases reported to CDC during December 2004 – July 2011). Nearly all of the reported C. gattii cases in the US are from Oregon, Washington, and California.[6,11] However, a small number of cases occur in other states 71% of clinical isolates in China are recovered from patienst without immune-suppression, and only 8.5% from patients with HIV (1980 -2006 global status). [6]

Patients with underlying neoplastic disease had shorter survival than AIDS patients even if death due to cryptococcal infection was distinguished from other causes, a result the authors attributed in part to the older age of patients with neoplastic disease. A population-based surveillance study covering the years 1992–2000 found that 21% of patients with non-HIV-associated cryptococccosis died on first admission or within 30 days (in the case of outpatients) compared with 11% of HIV-associated cases. Despite treatment with amphotericin B plus flucytosine, 34% of patients with C.gattii meningitis in Papua New Guinea died during their first admission, at a median of 8 days. In addition, over a third of survivors were left blind and many had hearing loss. A high rate of neurological sequelae has also been documented in series of C.gattii infections in Australia. [8, 11, 15].

While there is a wide range of literature and studies describing the incidences, manifestations, treatment, complications and relations with other diseases or conditions in the immunocompromised host (especially HIV where it is considered to be AIDS defining), there is very little literature to be found describing the condition in the immunocompetent individual or group. On the other hand, there is even less literature describing findings in peadiatric patients who are non HIV infected. Ethical approval was granted by the institutions involved and informed patient and parental consent was obtained before undertaking this case study.

To the authors' knowledge, there is no study conducted in Zambia that targets Cryptococcal infection in non-HIV co-infected individuals. A case of cryptococcosis was reported in 1969 by Bhagwandeen, Zambia. This was followed by a case of tracheal obstruction in 1977 by Patel K. F. and later still, (1983) Bisseru et al reported the first case of pulmonary Cryptococcus in a 19 year old Zambian who cared for pigeons.[P Mwaba]In addition, the case detection rate and the overall outcome of those in care are not documented. Studies of this condition in this particular group are few even at a global level, but are just as important as those conducted on HIV/ immunosuppressed clients in order to understand the

predisposing factors which would assist usin designingappropriate public health interventions that would reduce the current epidemic of cryptococcosis globally. Furthermore, with the current treatment regimens not being easily accessible to all (especially the developing world) due to the high costs, it emperative we take every opportunity to find more cost effective solutions to these and other medical conditions. This case study report is aimed at raising awareness on the presence of non HIV associated cryptococcosis in Zambia. The goal is to encourage more in depth studies firstly into the incidence and secondly into the conditions or contributing factors as the cause of a good number of CNS infections have at times gone undetermined in our health facilities or institutions. In other instances, despite making the diagnosis, its significance is not captured.

2. Case series

2.1 Case Number One

The case is of a 2 year old male who was brought to the hospital with a history of excessive sleeping for three months coupled with generalized body weakness.Second in a family of two. Born in lubalashi (an area endemic for Trypanosome carrying TseTse Fly and poor farming practices due to human animal conflicts). Pregnancy reached term and mother was HIV negative ante-Nataly. Home delivery but received the full cycle of vaccines (full immunization through outreach clinics). Attained all the milestones successfully up-to three months before admission when regression was noted.No previous admissions.Mother gives a drug history of Paracetamol, Folic acid, ferrous sulphate, Antimalarials (Coartem) – two cycles in last three months. Follow-up confirms medication was prescribed after a negative malaria testand based on elevated temperatures.The history of current condition is that of fever on and off for more than three months.Convulsed once (three months before admission).General body weakness for three months followed by failure to walk for three months. Excessive sleep during the daytime but failure to sleep during the night. Progressively poor appetite as child would fail to stay awake long enough to complete meals and consequently mild weight loss.Findings on admission were as follows;Body Weight - 11KGTemperature – 38.1 degrees Celsius. On inspection client was semi- conscious, very weak, apathetic, well perfused. On palpation neck was supple, moderate muscle spasticity, abdomen soft, normal organ size, negative for tenderness.Auscultation revealed heart sounds with normal rhythm, chest with clear breath sounds from both lung fields, bowel sounds present and normal.Provisional Diagnosis: Severe Malaria to rule out Second Stage Trypanosomiasis and Acute Flaccid Paralysis.

Labs: Rapid Diagnostic Test for malaria - Negative

Blood Slide for Trypanosomes and quantification for malaria – Both Negative

Diagnostic counselling and Testing for HIV – Non-reactive

Stool for AFP - Negative

Full Blood Count – non revealing

The child is commenced on empirical treatment for meningitis as investigations continue. After muchdeliberations with the parents on deteriorating condition a lumber puncture is authorized.

Additional Investigations: CSF microscopy – No Trypanosomes seen

- CAT reactive to Cryptococalneoformans
- Proteins:100mg/dl
- Glucose: 1.1 mmol/l

Final diagnosis, Cryptococcal Meningitis. Treatment with Amphotericin B is commenced. Child died day 3 on treatment.

2.2 Case Number Two

The case is of an 18 year old female (in high school) who is brought to the hospital with a history of back ache and generalized body weakness for one week (gradual onset). Also presents with an occipital headache for two days coupled with mild to moderate neck stiffness

which impedes her from turning sideways.Fever is present for seven days. On admission, the temperature is at 35.4 degrees Celsius, Blood pressure is at 109/75 millimeters of mercury, the pulse is 97 beats per minute. Physical examination is normal except formild pallor and the neck stiffness which gives us positive kernig and Brudzinskysigns. A provisional diagnosis of Meningitis querying the cause is made. A full blood count, diagnostic counselling and testing for HIV, Pregnancy test, urine analysis and Lumber puncture are ordered. In the meantime, intravenous antibiotics and analgesics are commenced. Findings from the laboratory reveal trace proteins and small leucocytes in urine. The pregnancy as well as HIV tests are negative.The Lumber Puncture reveals cryptococconeoformans(CAT reactive). FBC findings as follows; WBC-5.29 10^6/mm3, HGB-12.8 g/dl, HCT-39.2%, MCV-74 µm3, MCH-24.2 pg MCHC-32.6 g/dl, PDW- 14.1%. The white cell count was as follows: lym%- 27.9, mon%-7.2, Gra%-64.9.

2.3 Other Cases

Of note is that interviews of staff from a neighboring health facility revealed that three cases of cryptococcal meningitis in HIV negative adult males were recorded in the first half of this year. The cases presented with a variety of backgrounds and symptomatology. One of the cases is a known alcoholic with non-specific symptoms. The alcoholism could support the theory of predisposition due to some degree of immune compromise. Another case was a 19 year old who presented with headache, longstanding fever, projectile vomiting, neck stiffness, exolfthalmus and eventually blindness.

3. Discussion

3.1 Predisposition and Epidemiology

To begin with, Cryptococcus neoformans is an environmental saprophyte. The rarity of its isolation as a human commensal and of human-to-human transmission suggests that human infection is an accidental dead-end event in its life-cycle. In the environment and in clinical specimens, C.neoformans is found as a budding yeast. Cryptococcus neoformans can infect any organ in the body, but has a predilection for the lung and the CNS. The lung is the usual portal of entry and symptoms range from asymptomatic colonization to severe pneumonia. *C. neoformans* infections are extremely rare in people who are otherwise healthy; most cases occur in people who have weakened immune systems, particularly those who have advanced HIV/AIDS. The most common site for infection after the lungs is the Central Nervous System. The next most commonly involved organs in disseminated cryptococcosis include the skin, the prostate, and the medullary cavity of bones.(1,2,3)The diagnosis is supported by the epidemiological triage of the enabling environment, the opportunistic agent and the susceptible host as there is a strong element of underlying immunosuppression in the two cases based on the nutritional status in the area and the age. The host's susceptibility can be derived from the fact that the area of residence is prone to droughts and as such, there are times when the situation is so desperate that relief food has to be provided by the Disaster Management and Mitigation Unit. This is significant because it has a bearing on the nutritional status of the child in combination with the natural biological immaturity of the immune system in the under-five children. Despite the fact that the clients did not show obvious signs of poor nourishment, we can assume that at the very least they presented with some degree of micronutrient deficit which might have rendered the immune system inefficient to contain the agent. Of course, this cannot be proven at the moment.According to the Zambia Demographic Health Survey 2013 to 2014, overall, only 11 percent of children age 6-23 months are fed appropriately based on recommended infant and young child feeding (IYCF) practices. As a result, forty percent of children under the age 5 are stunted, 6 percent are wasted and 15 percent are underweight. As for the female patient, the major factor could be the prolonged exposure to the agent in the presence of large forest in the area of residence coupled with the possible underlying micronutrient deficit that is endemic to the area.

Despite the above mentioned, Cryptococcosis is not very common in the pediatric age group especially in the immunocompetent group. In fact, it is a rare disease in children worldwide, Zambia inclusive. The average age of infected children found in many study is quite similar. Cuba reports an average age of 5.4 years old (85.7% immunocompetent) with the lowest age while Thailand (all HIV+) and south Africa (91% HIV+) are tied at 7 years old. Coming in at 7.25 and 7.7 are China (all HIV-) and Brazil (most HIV-) respectively. Literature from surveillance studies in several countries support this statement. [12] The average age of infected children found in many study is quite similar. Cuba reports an average age of 5.4 years old (85.7% immunocompetent) with the lowest age while Thailand (all HIV+) and south Africa (91% HIV+) are tied at 7 years old. Coming in at 7.25 and 7.7 are China (all HIV-) and Brazil (most HIV-) respectively. [16,19,21]

3.2 Diagnosis

There is evidence of a subacute or chronic nature to the clinical manifestations characterized by low grade fevers. The child was attended to on several occasions at the local clinic. Malaria rapid diagnostic tests were conducted and treatment with antimalarial drugs and antibiotics was given despite tests giving negative results. The local facility has no capacity to conduct sophisticated tests that can isolate the agent.The second case on the other hand, presented with gradual apparition of signs and symptoms over a period of two weeks. From all of the references encountered, it is apparent that Meningitis is the most frequent manifestation of cryptococcosis. Infection of the subarachnoid space is accompanied by involvement of the brain parenchyma as evidenced in the child, and therefore the term meningoencephalitis may be more appropriate. Patients usually present with headache, fever, malaise and altered mental status over several weeks. From the two cases seen, there is no clear link to guide as to the clients' predisposition. The only common characteristic is that both are apparentlyimmunocompetent by testing HIV negative. Signs are often absent, but may include meningism. Meningism is the triad of nuchal rigidity (neck stiffness), photophobia (intolerance of bright light) and headache. It is a sign of irritation of the meninges, such as seen in meningitis and various other diseases. Usually, it is seen in concordance with other acute illnesses.[11] Papilloedema, cranial nerve palsies and other focal neurological deficit, and depressed conscious levels have also been seen. Complications such as raised intracranial pressure in the absence of ventricular dilatation may cause Nausea and vomiting,profound visual or hearing loss, Confusion, Lethargy, Obtundationand Coma which are common. Less commonly, patients may develop cognitive impairment and gait ataxia due to obstructive hydrocephalus with ventricular dilatation.[7,11,12,13] In first two cases, the findings were so non-specific that the diagnosis was highly dependent on the CSF findings.We also see clinical signs and symptoms attributable to the complication of raised intracranial pressure with projectile vomiting, exolfthalmus and visual impairment. Based on the characteristics of the presenting signs and symptoms, Cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis since clinical features are not specific.

3.3 Treatment

Cryptococcal meningitis is a common opportunistic infection in AIDS patients, particularly in Southeast Asia and Africa. Cases also occur in patients with other forms of immuno supression and in apparently immunocompetent individuals. Mortality from HIV-associated cryptococcal meningitis remains high (10–30%), even in developed countries because of the inadequacy of current antifungal drugs and the complication of raised intracranial pressure. In the USA, some studies have suggested that the outcome for non-HIV-associated cryptococcal meningitis may be worse than for HIV-associated infection. In cohorts of HIV-infected patients from sub-Saharan Africa and brazil, cryptococcosis has accounted for 13–44% of all deaths.[2,6,7]Optimal current therapy is with amphotericin B 0.7–1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks and

200 mg/day thereafter. Saline loading reduces amphotericin B nephrotoxicity.[6,7,10]For institutions that can afford to have a CT scan done, if there is no contraindication on the head scan, repeat lumbar puncture with drainage of cerebrospinal fluid (CSF) is recommended for patients with very raised CSF opening pressure. Expansion of antiretroviral programmes raises the prospect of transforming the long-term prognosis of immuno supressed patients, provided that they survive the acute phase of the illness. For the immunocompetent patient, more studies are needed to understand the pathogenesis as well as to define more appropriate fungicidal drug regimens and to improve the treatment of raised intracranial pressure. The recommended treatment for CM is a combination of AmB and flucytosine. The optimal dosing of AmB remains unclear. Liposomal AmB is associated with less adverse events than AmB and may be useful in selected patients where resources allow. Future research into the management of cryptococcal meningitis in resource-limited settings should focus on the most effective use of medications that are available in these settings. Flucytosine in combination with AmB leads to faster and increased sterilisation of CSF compared to using AmB alone. As Flucytosine is often not available in developing countries, policy makers and national departments of heath should consider procuring this drug for HIV treatment programmes.[13,15,19,20]

3.4 Possible Differentials

The areas in question (Rufunsa and Chongwe Districts) are endemic to quite a number of conditions that might paint a picture similar to that observed in the cases under discussion. The area is considered to be remote, in the case of Rufunsa, as well as rural for Chongwe. It is also important to note that the two districts are located in a valley surrounded by thick vegetation and mountain ranges. The heavy tropical climate provides optimal conditions for breeding of mosquitoes. A review of facts in the provincial health information system shows that the two districts are rated as second and third highest respectively in the province out of eight districts for malaria Incidence. The mountain ranges are housing wild life which has created some challenges for food security and morbidity in the community. This compromises the nutritional status of the community at large. Furthermore, the presence of game areas brings about the presence a reservoir (the animals) for the Trypanosome parasite and the vector (Tsetse Fly) which transmits the parasite to human beings. With such a picture, both types of Cryptococcus that have been isolated in humans, namely neoformans and gatti have more than sufficient favourable environmental factors to thrive.

We can exclude Severe or Cerebral malaria as a possible diagnosis as the malaria rapid test (RDT) and blood slide were both negative on several occasions. Moreover, malaria generally has a more acute course in children which is coupled with a more aggressive form of manifesting signs and symptoms. There is also the presence of very high temperatures of 39 degrees or higher once it takes on the neurological phase. Anaemia is another common sign with enlargement of the spleen. This can be acute or chronic.

Another endemic condition to the area is Trypanosomiasis (Neglected Tropical Disease). Just like Cryptococcus infection, it presents with a chronic sub-clinical course which is characterized by low grade fever and punctuated by CNS manifestations towards the end stages. For the past three years, it has been confirmed in 11 adults and 1 child of 18 months (an average of four cases per year) with a history of staying in the game areas or conducting some hunting activities. The cases under discussion had no positive contacts. Moreover, a targeted search for the trypanosomes in the lab investigations such as blood slides and Cerebral Spinal Fluid yielded negative results.

Accute flacid paralysis is a highly infectious disease caused by Polio virus. It invades the nervous system, and can cause total paralysis in a matter of hours. The virus is transmitted by person-to-person spread mainly through the faecal-oral route or, less frequently, by contaminated water or food and multiplies. Manifestation includes fever, fatigue, headache, vomiting, stiffness of the neck and pain in the limbs. One in 200 infections leads to irreversible paralysis (usually in the legs). Among those paralysed, 5% to 10% die when their

respiratory muscles get immobilized. (WHO Fact Sheets 2015) The incidious nature of the symptomatology in the child ca rule out acute paralysis. Further, only Afghanistan and Pakistan are endemic for the disease today.

We could consider retroviral disease encephalitis (RVD) as another possible diagnosis. The condition is excluded due to the fact that the child tested negative for Human immunodeficiency virus on numerous occasions both at the local clinic and the referral hospital. Further, the lab findings did not indicate any predilection of the white cells towards a viral infection.

Is it correct to assume that there was a form of immune-incompetence brought on by micronutrient deficiency coupled with the natural immaturity of the system in children below the age of five years? If that is not the case then what could have predisposed the child to the infection or better still, why was the child's immunity not able to contain the infection? Could this mean that the fungus is evolving or are we just missing these cases due to the fact that we are not searching (a loop hole that needs to be sealed in order to fully understand how this agent functions?). The questions are many and the answers not quite forthcoming. Some answers lie in the survivors of the infection as they can accord us a chance to glean some insight into their immunity and its failure as a defense. Additionally, we might also be able to study the strain of the fungus found in these individuals in search of possible changes to its previously studied genetic makeup as well as physiology.

In conclusion, Cryptococcal meningitis is the most common life threatening fungal infection in patients with AIDS. The frequency of cryptococcal meningitis has been on the increase since the discovery of HIV but there's been a halt of this trend with the introduction of Highly Active Antiretroviral Therapy (HAART). However in countries where patients have poor access to HAART, the Frequency of Cryptococcal meningitis is still high. Furthermore, it is clear that despite all the progress made in documenting the process of infection, manifestation and management in the immunocompromised, we still have much to discover on the process in the non-immunocompromised patient. More detailed studies are required in order to make the necessary advances for the apparently immune competent patient. In order to do so, we must have a high index of suspicion and actively search for the fungal agent in any patient found with meningism in our institutions.

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