CYTOMEGALOVIRUS RETINITIS AND CRYPTOCOCCUS MENINGITIS WITH PAPILITIS IN PAEDIATRIC AIDS PATIENT

Chan Hui Tze 1,2, Vanessa N. Mansurali 2, Wan-Hazabbah Wan Hitam 1, Liza Sharmini Ahmad Tajudin 1

1 Department of Ophthalmology, School of Medical Sciences, Health Campus Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia
2 Department of Ophthalmology, Hospital Pulau Pinang, 11000 Pulau Pinang, MALAYSIA

Corresponding Author: Chan Hui Tze, Department of Ophthalmology, School of Medical Sciences Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, chanhuitz@gmail.com

ABSTRACT

Background: The incidence of ocular complications in HIV-infected patients varies from 42% to 75% and some of these complications may lead to blindness. Here we report a rare case of retroviral disease with cytomegalovirus (CMV) retinitis in one eye and papillitis secondary to cryptococcus meningitis in the other eye.

Case Report: A 14 year old Malay girl who was diagnosed with AIDS since birth through vertical transmission presented with fever, headache, seizure and chronic poor vision in the right eye for about 8 months duration. She was on antiretroviral therapy (HAART). Visual acuity in the right eye was only perception to light and in the left eye was 6/9. Both anterior segments were unremarkable. Fundoscopy of the right eye showed generalised shallow retinal detachment and left swollen hyperaemic disc. Computed tomography (CT) scan of the brain was normal. Lumbar puncture opening pressure was normal as well. A diagnosis of retroviral disease with cryptococcal meningitis, right advanced CMV retinitis and left papillitis was made. Patient was treated with HAART regime, ganciclovir, amphotericin B, flucytosine and fluconazole. The papillitis responded well to treatment. However, the CMV retinitis persisted.

Conclusion: In conclusion, AIDS patients are susceptible to multiple opportunistic infection that may co-exist with different severity in either eye. Prompt diagnosis and early medical intervention may preserve vision and improve life expectancy.

Keywords: paediatric HIV infection, cytomegalovirus retinitis, cryptococcus papilitis, cryptococcus meningitis
1.0 Introduction

There are 3.4 million HIV-infected children worldwide and reports suggest that every hour about 30 children die as a result of AIDS according to World Health Organization Progress report 2011. Ocular manifestations among HIV infected children are diverse and global incidence varies from 7% to 75% (Yonaba et al. 2016). According to UNAIDS global report 2013, it was estimated that 2 million children under 15 years old were infected by HIV in Sub-Saharan Africa in 2012, which was almost 62% of the world total population in this age group. Ocular manifestations may be observed at all stages of immuno-depression and may affect any eye segment, but the incidence and the gravity of lesions depend on immune status (Esposito et al. 2006, Nsiangani et al. 2013). With the advent of drugs to control HIV infection, the incidence of complications has reduced but has not been eliminated. We report a rare case of CMV retinitis in one eye and papillitis in the other eye in a paediatric patient with retroviral disease.

2.0 Case Report

Our patient was a 14 years old Malay girl with vertically transmitted retroviral disease detected at 6 years of life. She and her two younger siblings were screened for retroviral disease when their mother succumbed to AIDS complications. She was started on HAART regime upon diagnosis but the compliance was poor. Her CD4 count has been decreasing from 698 cells/µL at time of diagnosis to 19 cells/µL at present. Her viral load has been steady around 250000-350000 copies/mL. She was also suspected to have resistance to her pre-existing HAART and hence started on new HAART regime. She presented with fever, seizure, headache, photophobia, and blurring of vision in the right eye for 8 months. Left eye vision was fairly good. Systemic examination was unremarkable other than patient appeared cachexic. Ocular examination revealed visual acuity in right eye was perception to light and visual acuity in left eye was 6/9. There was presence of relative afferent pupillary defect over the right eye. Both anterior segments were unremarkable. Right fundus showed a pale disc with large area of retinitis and haemorrhages. There was generalised retinal detachment which suggested advance CMV retinitis [Figure 1]. Left eye fundus showed optic disc swelling with no evidence of retinitis or vitritis [Figure 2]. Computed tomography of the brain was normal. There was no sign of hydrocephalus, subdural effusion, empyema, infarction or abscess. Lumbar puncture showed opening pressure of 11mmHg. Cerebral spinal fluid (CSF) cytology was positive for cryptococcal neoformans. Blood for CMV polymerase chain reaction was also positive. Investigations for herpes simplex virus, varicella-zoster virus, toxoplasma, and mycobacterium tuberculosis were negative. Diagnosis of cryptococcal meningitis, right eye advanced CMV retinitis and left eye cryptococcal papilitis was made. She was commenced on intravenous ganciclovir, amphotericin B, flucytosine and fluconazole. After one month of treatment, her left eye visual acuity improved to 6/6 with resolution of optic disc swelling. The right eye fundus remained the same. She was discharged after one month and defaulted subsequent follow up.
**Figure 1**: Right pale disc with generalised area of retinal necrosis.

**Figure 2**: Left hyperaemic swollen disc
3.0 Discussion

There is a lesser prevalence of ophthalmic manifestations of human immunodeficiency virus (HIV) infection in children as compared to adults as described in various studies (Kestelyn et al. 2000), which also manifest differently in them (Esposito et al. 2006). CMV and other infections (tuberculosis, toxoplasmosis, cryptococcosis) are less likely to develop in children because they have not yet been infected with these organisms, unlike adults in whom reactivation of potent infection occurs when the immune system deteriorates (Lepage and Hitimana 1991).

Because mother to child transmission is the main mechanism of paediatric HIV acquisition, most children present in infantile period. Nevertheless, the age of presentation may be variable. In HIV-1-infected children, the most frequently observed clinical signs were chronic cough, failure to thrive, and generalised lymphadenopathy, which also were reported among the most frequent HIV-related conditions in other developing countries (Lepage and Hitimana 1991). The Treat Asia Paediatric HIV observational database reported perinatal exposure incidence to be 94.1%. Infants with perinatal infection are at higher risk for early mortality than those infected later through breastfeeding. Maternal variables such as viral load, advanced disease, co-infections, delay or non-use of antiretroviral therapy at the beginning or during pregnancy influence risk of HIV maternal to child transmission. Vertical HIV transmission rates can be reduced to level below 2% if women living with HIV have a suitable attendance during pregnancy with the use of antiretroviral therapy and reduction of the viral load (Cooper et al. 2002). With prevention-of-mother-to-child-transmission efforts, the number of new congenital HIV infection cases dropped from 1650 to 107 (from 1991-2013) in the USA.

Several interactions seem to exist between CMV and HIV. HIV induces immunosuppression and facilitates all herpes virus development, including CMV. On the other hand, CMV promotes HIV pathogenicity, either by introducing into the cell its transactivation proteins, that activate HIV proviral DNA, or by stimulating production of inflammatory cytokines which activate HIV DNA. Thus, CMV acts as a cofactor for HIV, with higher viral production and a more rapid progression to Acquired Immune Deficiency Syndrome (AIDS). Cytomegalovirus retinitis remains the most common AIDS-related, ocular opportunistic infection and can develop in up to 40–50% of AIDS patients (Banker and Patel 2002). Disease may be unilateral to start with, but up to 52% of patients will eventually develop bilateral disease (Kuppermann et al. 1993). Visual loss is mainly due to direct extension of retinitis to the macula or optic nerve head, or retinal detachment. The Longitudinal Study of the Ocular Complications of Acquired Immune Deficiency Syndrome (AIDS) showed that the ocular findings in patients with newly diagnosed CMV retinitis in the post-HAART era resembled those prior to the introduction of HAART. The choice of anti-CMV therapy is usually based on efficacy and tolerability profiles, pharmacologic considerations, and quality of life issues. Comparison studies of intravenous ganciclovir with oral ganciclovir and intravenous foscarnet (The Studies of Ocular
Complications of AIDS Research Group 1996) or cidofovir (Douglas 2001) have failed to show significant differences between drug choices. For most patients, valganciclovir is the drug of choice, due to its lower complication rate, as well as convenient oral administration. Our patient was treated with intravenous ganciclovir due to high cost and limited availability of valganciclovir. CMV-infected child is at substantial risk for general intellectual deficit regardless of auditory or visual involvement. Common complications of CMV infection include retinitis, pneumonitis, colitis, esophagitis, hepatitis, cholangitis, encephalitis, and myeloradiculopathy.

Cryptococcus neoformans is ubiquitous encapsulated saprophytic yeast found in soil. Two species, transmitted by inhalation, are the principal human pathogens: Cryptococcus neoformans and Cryptococcus gattii. Cryptococcus neoformans infection is the most common fungal infection of the central nervous system (CNS) in advanced HIV and AIDS patients (Curtis and Aisha 2016). HIV-infected patients are mainly at risk of cryptococcosis when they become very immunosuppressed and their CD4 count drops below 100 cells/µL. Two patterns of visual loss appear to occur in HIV-infected patients include rapid onset of visual loss and gradual visual deterioration. Traditionally, the rapid onset of vision loss (3 days or less) have been thought to have different aetiologic mechanisms. The first is thought to result from direct infiltration of the optic nerves or adhesive or inflammatory arachnoiditis (Bach et al. 1997), while the second occurs from uncontrollable long-term intracranial hypertension (Rex et al. 1997). Forty percent of patients with cryptococcus meningitis have ocular involvement (Kestelyn et al. 1993). Intraocular cryptococcus may takes the form of chorioretinitis, multifocal choroiditis, neuroretinitis, vitritis, papilitis or endophthalmitis (Sheu et al. 1998). Optic nerve oedema from increased intracranial pressure with risk of optic atrophy is likely a more common complication of central nervous system cryptococcosis than intraocular invasion (Kestelyn et al. 1993), but is otherwise in our case. Medical treatment with intravenous amphotericin B and oral fluconazole has a guarded prognosis and permanent neurological and ophthalmic sequelae is common (De Socio et al. 2011). The Infectious Diseases Society of America (IDSA) and WHO guidelines emphasise the importance of potent fungicidal drugs during induction therapy, because the rate of fungal clearance from the CSF during the first 2 weeks, known as early fungicidal activity (Brouwer et al. 2004), predicts 10-week survival (Bicanic et al. 2009), and CSF sterilisation by 14 days predicts long-term prognosis (van der Horst et al. 1997). We would like to highlight that omission of flucytosine, which is still not widely available in developing countries, has been associated with higher rates of mortality (Day et al. 2013), treatment failure (Dromer et al. 2008), and late relapse (Saag et al. 1999). The recent results from the ACTA trial study 2018 (Advancing Cryptococcal meningitis treatment for Africa) suggested the shortest and simplest effective regimens, 1 week of amphotericin B plus 2 weeks of flucytosine as the most effective option for induction therapy for patients with HIV-associated cryptococcal meningitis in resource-limited settings, or alternatively oral combination of fluconazole plus flucytosine. It is apparent that the optimal treatment modalities for cryptococcal meningitis has yet to be determined. Visual complications are not uncommon in cryptococcal meningitis, and once vision loss occurs, it is often
irreversible regardless of control of infection or intracranial pressure. Visual complaints in cryptococcal meningitis should be considered a potentially poor prognostic sign. Other complications of cryptococcal infection include pulmonary cryptococcosis, cutaneous cryptococcosis and adrenal insufficiency secondary to cryptococcal invasion of adrenal gland.

4.0 Conclusion

Paediatric HIV infection is a generally feared and missed clinical condition due mainly to unfamiliarity. With the introduction of HAART, paediatric HIV infection has switched from a highly lethal disease to a chronic disorder with prolonged life expectancy. Although mostly vertically transmitted, HIV infection may be diagnosed throughout the childhood. Frequently encountered signs and symptoms may be the reason for admission. High clinical suspicion together with detailed anamnestic data and physical findings constitute the basis for paediatric HIV diagnosis. The pattern of ophthalmic manifestations of HIV in paediatric patients are different from that found in adults. Thus, it becomes challenging to screen carefully and thoroughly every HIV positive patient in order to pick up subtle, unconventional and unexpected manifestations. Patients with visual disturbances or unremitting ophthalmic symptoms, regardless of CD4 cell count should be evaluated by an ophthalmologist. The ultimate goal for the prevention of paediatric HIV infection is an effective vaccine that can be administered at birth. Even then, it may be envisioned that this vaccine would be needed to be given in conjunction with a period of HAART in infected neonates in order to prevent the immune destruction that follows persistently high levels of viral replication.
Acknowledgement

Ophthalmologists and staffs of Ophthalmology Department, Hospital Universiti Sains Malaysia and Hospital Pulau Pinang, Malaysia

Declaration

The authors declare no conflict of interests. The authors are responsible for the content and writing of the paper.

Authors contribution

Author 1: Wrote the manuscript
Author 2: Manage the case
Author 3: Provided critical feedback
Author 4: Supervised the whole process

References


