MALARIA AND THE EYE

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SUMMARY

Objective: To review and highlight the ocular complications of malaria and antimalarial treatment.

Method: Information was obtained through a review of current literature and Internet search.

Results: Ocular complications in malaria result either from the direct effects of red cell invasion and destruction by the parasites and the host's reaction to it, or indirectly from systemic complications of malaria or the side effects of drugs used in its treatment or prophylaxis.

These complications range from lagophthalmos, posterior subscapsular lens opacities to disc oedema, bull's eye maculopathy, and retinal haemorrhages, among other posterior segment changes, as well as neuroophthalmic complications such as cortical blindness and nystagmus

Conclusion: Blindness or visual impairment can result from malaria. It is recommended, therefore, that the eye should be frequently evaluated during the management of malaria, especially in severe cases.

Key words: malaria, eye, ocular complications, retinal haemorrhage, cortical blindness, nystagmus

INTRODUCTION

Malaria is caused by minute parasitic protozoa of the genus *Plasmodium*.[1] It is transmitted by the bite of the female anopheles mosquito. It remains one of the biggest health problems in large parts of the world, and is actually the most important parasitic disease of humans.[1]

Approximately 300 million people worldwide, spread over 103 endemic countries, are affected by malaria.[2] In sub-Saharan Africa alone, it is currently estimated that there are more than 150 million clinical cases annually, and that about 2 million people die from the disease every year.[3] Today, malaria remains, as it has been for centuries, a major burden on tropical communities and a danger to travellers.

Irrespective of a doctor's area of speciality he/she is very often faced with the diagnosis and treatment of patients with malaria. From time to time, the ophthalmologist is invited to evaluate the ocular health status of a patient during or after the course of a malarial attack.

Eye abnormalities in malaria patients have been described by various workers since 1879.[4] While some have found these changes to be of great prognostic significance,[5-6] others consider them to be indicators of severity,[7-8] and others still have found them to be of no specific significance.[9]

In this paper, the epidemiology, pathogenesis and ocular complications of malaria and antimalarials are discussed.

EPIDEMIOLOGY

Malaria is found mainly in regions between latitudes 60°N and 40°S throughout most of the tropics and subtropics – excluding the Mediterranean littoral, South America and Australia.[10,11]

Four species of the genus *Plasmodium* cause malaria in humans. These are *Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale* and *Plasmodium malariae*. Of these, *P. falciparum* is the most important, both in terms of the number of clinical cases and the severity of the disease. It is the most widespread and dangerous. If left untreated, it can lead to cerebral malaria. Almost all deaths from malaria are caused by *P. falciparum*.[12]

The differentiation of the species depends on the morphology and staining of the parasites and associated changes in the containing cells.[10]

Plasmodium falciparum predominates in sub-Saharan Africa, New Guinea, and Haiti. *P. vivax* is more common on the Indian subcontinent and in South America. The prevalence of these two species is roughly equal in Eastern Asia, Oceania and South America. *Plasmodium malariae* is found in most endemic areas, especially in sub-Saharan Africa (particularly West and Central Africa), however, it is much less frequent. *Plasmodium ovale* is relatively unusual outside Africa, although some

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cases are now being identified in other regions (e.g., in the southern states of India). [13]

It is, however, important to recognize that with the relative ease and speed of modern travel and migration, 'imported' cases of malaria may present in any country. This explains the growing trend of 'airport malaria'.

The epidemiology of malaria may vary even within small geographic areas. The major epidemiologic determinants are the immunologic and genetic make-up of the population, the species of parasite and mosquito in the community at risk,[14, 15] the level of rainfall, the temperature, the distribution of mosquito breeding sites, the use of antimalarial drugs, and the application of other control measures that could decrease transmission.[16]

PATHOGENESIS

Malaria parasites are transmitted from one person to another by the female anopheline mosquito. The male anopheles mosquito does not transmit the disease as it feeds only on plant juices. There are about 380 species of the anopheles mosquito, but only about 60 are able to transmit the parasite. Like all other mosquitoes, anophelines breed in water, each species having its preferred breeding grounds, feeding pattern and resting place. Malaria in humans is attributable to the direct effects of red cell invasion and the destruction and the host's reaction to this process.[2]

A female anopheline mosquito, which is infected, bites a human and injects primitive malaria parasites called sporozoites into the blood stream before taking a blood meal. These sporozoites circulate in the blood for about 30 minutes and then enter the parenchymal cells and multiply, thereby beginning a period of asexual reproduction. This stage is known as pre erythrocytic schizogony. After about 5-12 days (depending on the species),the sporozoites develop into merozoites within the liver cells. The liver cells (hepatocytes) eventually burst, discharging thousands of merozoites into the blood stream, which subsequently enter the red blood cells. This initiates the erythrocytic cycle.

Within the red cells, the parasite continues to multiply through asexual cycles. The plasmodium first appears in the red cells as a small speck of chromatin surrounded by scanty cytoplasm, and soon becomes a ring-shaped trophozoite. As the parasite develops, pigment particles appear in the cytoplasm, and the chromatin is more prominent. Chromatin division then proceeds, and when complete, forms the mature schizont containing daughter merozoites. The parasitized red blood cell now ruptures, releasing merozoites, the majority of which re-enter the erythrocytes to re-initiate erythrocytic schizogony.

Each release of merozoites coincides with the development of fever, whose periodicity depends on the species of parasite. In *P. falciparum*, the erythrocytic cycle takes 36-48 hours, releasing up to 32 'daughter' merozoites (subtertian). In *P. vivax* and *P. ovale* infections, this takes 48 hours (tertian); a proportion of these in prehepatic forms do not divide immediately, but remain dormant as hypnozoites, for months or even years before developing into merozoites. Thus, the first attack of clinical malaria may occur long after the patient has left the endemic area. In *P. malariae*, the release occurs every 72 hours (quartan).

In response to some unknown stimuli a number of the merozoites released after erythrocytic schizogony develop into male and female gametocytes. These are long-lived and are not associated with illness in man. They provide the reservoir of infection enabling mosquitoes to transmit malaria. They remain within the cell for up to 120 days. These gametocytes circulate in the blood and are taken up by the female anopheline mosquito during a blood meal. The male and the female gametocytes fuse in the mosquito's stomach and form zygotes.

The zygotes mature to form ookinetes, which penetrate and encyst in the mosquito's gut wall. The resulting oocysts develop over a period of days by asexual division, bursting to liberate many sporozoites. The sporozoites migrate to the salivary glands and are ready to be injected/inoculated into man at the mosquito's next blood meal.[10,11,17,18]

Other Routes of Transmission: Malaria may also be transmitted by blood transfusion or by needle sharing between infected intravenous drug users.[11,13] *P. falciparum* and *malariae* are the most common aetiologic agents in such cases. There is no pre-erythrocytic stage involved, so the incubation period is often shorter. Transplacental infection may also occur.[18,19]

Ocular changes in malaria result from the following:[20-23]

a. Direct effects of red cell invasion and destruction by the parasites and the host's reaction to this;

b. Vascular obstruction by parasitized erythrocytes;

c. Indirect effects of reduction of vitamin A stores;

d. The depressive effect of malaria on immunity leading to malignant transformation of B-cells with development of Burkitt's lymphoma and, reactivation of viral infections;

e. The systemic complications of severe malaria which include disseminated intravascular coagulopathy, Guillain Barré syndrome, renal failure and hepatic encephalopathy.

f. The complications of drugs used in its treatment or prophylaxis.

OCULAR CHANGES IN MALARIA

Adnexal Complications

Lids[24]

- Lagophthalmos
- Paralytic ectropion
- Lid retraction
- Poor blink mechanism

The above are all signs of facial nerve palsy which can be a complication of malaria. The pathogenesis of facial nerve paralysis is not precisely understood (see cranial nerve palsies below).

Conjunctiva

Pallor:[20] This is a sign of anaemia. It is picked up on the tarsal conjunctiva. The pathogenesis of the anaemia is multifactorial.

a. Obligatory destruction of red blood cells containing parasites at merogony;
b. Accelerated destruction of non-parasitised RBCs, parallels disease severity;
c. Bone marrow dysfunctions – reticulocyte count is low in acute phase;
d. Lowered threshold for splenic clearance of abnormal erythrocytes. Red blood cell survival is decreased;
e. Decreased concentrations of interleukin-10** (IL-10) and increased concentration of tumour necrotic factor-alpha** (TNF-α). IL-10 has an inhibitory effect on TNF-α, which contributes to bone marrow suppression and RBC destruction.

The role of antibodies (Coomb's positive) in anaemia is unresolved.

Anterior Segment Complications

Sclera

Jaundice[20] is one of the ocular abnormalities that occur as a result of malaria. It appears to have haemolytic, cholestatic and hepatitic components. Hyperbilirubinaemia in malaria could result from the following factors:

a. Intravascular haemolysis of parasitized erythrocytes;
b. Hepatic dysfunction;
c. Microangiopathic haemolysis associated with disseminated intravascular coagulopathy (DIC);
d. Liver function impairment due to associated gram negative septicaemia;
e. Concomitant viral hepatitis.

**Interleukins and tumor necrosis factors are types of cytokines. Cytokine is a generic term for any soluble polypeptide mediator that is synthesized and released by cells for the purposes of intercellular signalling and communication.[25]

Posterior Segment Complications

Vitreous

- Haemorrhage: This occurs as a result of disseminated intravascular coagulopathy.[20]

Disc

- Papilloedema

Retina

- Haemorrhages:[5, 9, 26-28] In severe malaria multiple haemorrhages are seen. These could be flame-shaped, of the Roth's spot type, dot and blot or boat-shaped. Retinal haemorrhages in malaria could be superficial, deep or both.

Haemorrhages and papilloedema are found more frequently in cerebral malaria than in severe noncerebral and uncomplicated malaria, but are not associated with increased mortality.

The number of retinal haemorrhages has been shown to correlate with cerebral haemorrhages at postmortem examination. These retinal haemorrhages could be the complication of anaemia.

- Oedema
- Cotton wool spots

Pathogenesis

As the malarial parasite matures inside the RBC, the RBC becomes progressively more spherical and rigid. The parasitized RBCs can cause occlusion of a feeder arteriole and capillaries. An oedematous change then occurs in the inner retinal layers due to ischaemia. This results in the formation of cytoid bodies. The cytoid body is only a specific and transient alteration of nerve fibres in the early stage of the ischemic lesion in the retina. They are seen clinically as cotton wool spots.

Cotton wool spots are also a complication of anaemia.

- Whitening[29]

The pathophysiology of retinal whitening remains unclear, although intracellular swelling in response to hypoxia is suspected.

Severe anaemia in malaria is likely to be associated with high concentrations of sequestered, parasitized erythrocytes within the microvasculature, a condition which is thought to cause retinal vascular occlusion.

Similarly, high densities of rapidly metabolizing parasites in the retinal vasculature may produce relative hypoxia leading to intracellular oedema. This has been proposed as a mechanism which causes retinal whitening.

Vessels[27]

- Venous dilation
- Venous tortuosity

The above vascular changes are reactions to retinal ischaemia. They are also seen in anaemia.

• Retinal vessel discolouration

Retinal vessels may become pale orange or white, including whitening of the capillary network. The vessel whitening can be in the form of delineation of the central blood column.

Vessel whitening may be due to the presence of cytoadhered or sequestered erythrocytes, in which haemoglobin has been metabolized by intracellular parasites.

Sequestration of dehaemoglobinized, parasitized erythrocytes has been shown on histopathologic examination to occur in the retinal vessels of the eyes with vessel whitening.[30]

Macula

Whitening with sparing of the foveola.[27, 28]

Cranial Nerve Palsies in Malaria[10, 11]

- Facial nerve palsy
- Retrobulbar optic neuritis
- Trigeminal neuralgia

The *pathogenesis*: of these mononeuritic syndromes is not precisely understood but possibilities include:[10, 11, 13]

a. Parasitic emboli obstructing the vasa nervorum,
b. Liberation of neurotoxins from the parasite and/or
c. Metabolic or nutritional disturbances

Sudden Loss of Vision in Malaria

Possible causes of sudden loss of vision in malaria include:

a. Vitreous haemorrhage[20]
b. Cortical blindness.[20] Convulsions, which could occur in severe malaria either from fever or encephalopathy, can result in cortical blindness.

Pathogenesis: Cortical blindness in children is most commonly caused by hypoxia/ischaemia of the cerebral cortex. Regardless of the cause, a seizure causes cerebral hypoxia.

Neuroophthalmic Signs of Cerebral Malaria[20]

a. Dysconjugate gaze (internuclear ophthalmoplegia) is a common finding; the eyes are usually divergent with normal doll's eye movement;
b. Corneal and conjunctival reflexes are usually intact;
c. Pupils are symmetrical and react normally to light;
d. Papilloedema is rare;
e. Retinal haemorrhages are sometimes seen.

Following an attack of cerebral malaria, these ophthalmic conditions[20] could result:

a. Cortical blindness
b. Isolated 6th nerve palsy
c. Ocular bobbing
d. Nystagmus (vertical and horizontal)
e. Sudden loss of vision from vitreous haemorrhage

Burkitt's Lymphoma and Malaria[23]

Burkitt's lymphoma is named after Denis Parsons Burkitt, who mapped its peculiar geographic distribution across Africa. It is endemic in certain regions of equatorial Africa and other tropical locations between latitudes 10° south and 10° north. It is a high-grade B-cell neoplasm and has 2 major forms: the endemic (African) form and the non endemic (sporadic) form.

There is a strong association between Burkitt's lymphoma (the African form) and malaria. The lymphocytes have receptors for Epstein-Barr virus (EBV) and are its specific target. Progression of EBV infection in B lymphocytes is controlled by virus specific cytotoxic T cells. In the African form, the hosts are believed to be unable to mount this appropriate immune response to primary EBV infection. This may predispose the patient to malignant transformation (excessive B cell proliferation). Malaria is believed to be responsible for this reduced immunity.

The African form most often involves the maxilla or the mandible. Due to the involvement of the maxilla it is a cause of non-axial proptosis in children.

Xerophthalmia and Malaria[21]

Anorexia, vomiting and diarrhoea (which are sometimes symptoms of malaria), with the resultant low intake as well as poor absorption of food, could further predispose a malnourished child with low vitamin A stores to vitamin A deficiency and xerophthalmia.

Signs of vitamin A deficiency/xerophthalmia include the following:

a. Nyctalopia is often the earliest symptom of hypovitaminosis A.
b. Xerophthalmia fundus, a rare associated abnormality, features yellow-white spots in the peripheral fundus.
c. Prolonged vitamin A deficiency leads to external involvement, including xerosis (dryness of the conjunctiva and cornea), metaplastic keratinization of areas of the conjunctiva (Bitot spots), corneal ulcers and scars, and eventually, diffuse corneal necrosis (keratomalacia).

The World Health Organization classifies the ocular surface changes into three stages:

- Conjunctival xerosis, *without* (X1A) or with (X1B) Bitot spots
- Corneal xerosis (X2)
- Corneal ulceration, with keratomalacia involving less than one third (X3A) or more than one third(X3B) of the corneal surface.

Viral Ocular Infections and Malaria[31]

Systemic immunocompromise following a severe attack of malaria can predispose an individual to ocular infection with herpes simplex or herpes zoster infection.

HSV: The two serotypes (1 and 2) affect the eye but type 1 causes the majority of the eye infections. On reactivation of the virus, the following ocular signs could result: blepharitis; conjunctivitis with or without punctate epithelial keratitis; keratitis (dendritic epithelial; geographic epithelial; stromal); trabeculitis; iridocyclitis

Varicella-zoster virus: Common ocular complications of trigeminal zoster are epithelial keratitis, marginal corneal infiltrates, stromal keratitis and neurotrophic keratopathy.

Guillain-Barré Syndrome (GBS) and Malaria[22]

Guillain-Barré syndrome (GBS) can complicate severe malaria. This syndrome is an acute – frequently severe and fulminant – polyradiculoneuropathy that is autoimmune in nature. It manifests as a rapidly evolving areflexic motor paralysis, with or without sensory disturbance. The ophthalmic signs of GBS are:

a. Cranial nerve palsies, especially of the facial nerves
b. Papilloedema: This papilloedema is possibly related to impaired cerebrospinal fluid (CSF) resorption because of the elevated protein content

Miller-Fisher syndrome: This is a sub-type of GBS. Its manifestations are as follows: external ophthalmoplegia often with pupillary paralysis, ataxia, tendon areflexia and diffuse cranial nerve involvement.

Coagulopathy and Malaria[20]

Severe haemorrhage is seen in 5% of severe malaria as a result of coagulopathy and thrombocytopenia. There might be bleeding into tissues like the subconjunctiva and vitreous.

Pathogenesis of the haemorrhage: In severe malaria, there is accelerated coagulation cascade activity with accelerated fibrinogen turnover, consumption of antithrombin 111, and increased concentration of fibrinogen degradation products (FDP). Red blood cells containing parasites and released cytokines are procoagulant. Prothrombin time (PT) and activated partial prothrombin time are prolonged.

Thrombocytopenia is caused by increased splenic clearance. Platelet turnover is increased. The role of platelet-bound antibodies is controversial.

Ocular Complications of Antimalarial Drugs[32-33]

Chloroquine and hydroxychloroquine[47]

Chloroquine has an affinity for pigmented (melanin-containing) structures, which may explain its toxic properties in the eye.

Cornea

Corneal deposits, limited to the basal epithelium, are seen as tiny white dots that become yellow and then golden brown with continued use of the medication. The deposition pattern ranges from a fine diffuse punctate appearance, to radial or whorl-like lines converging just inferior to the central cornea, to coalesced and darkened lines.

Corneal sensation is decreased in approximately 50% of patients taking chloroquine.

Lens

Chloroquine, but not hydroxychloroquine, may cause white, flake-like posterior capsular lens opacity.

Uvea (ciliary body)

Chloroquine, but not hydroxychloroquine, may decrease accommodation.

Retina

The fundus appearance may remain entirely normal, even after scotomas have developed. Early changes include irregularity (mild stippling or mottling) in the macular pigmentation and blunting (reversible) of the foveal reflex. Examination with a red-free filter may enhance detection of these changes.

Later, the central irregular pigmentation may be surrounded by a concentric zone of hypopigmentation, usually oval and more prominent inferiorly to the fovea. This condition is often bilateral, although asymmetry is not uncommon.

If the treatment is not halted and the toxicity progresses, the classic bull's eye maculopathy appears. Further prolonged exposure to the quinolones may lead to more generalized pigmentary changes.

End-stage retinopathy presents with peripheral pigment irregularity and bone spicule formation, vascular attenuation, and optic disc pallor. It is sometimes mistaken for retinitis pigmentosa.

Fansidar / Maloprim / Pyrimethamine[33]

These sulpha-containing drugs can cause Stevens-Johnson syndrome. Stevens-Johnson syndrome (erythema multiforme major) is an acute, generally self-limiting, severe, mucocutaneous, vesiculobullous disease, probably caused by a hypersensitive reaction to certain drugs, including the sulpha-containing drugs. The basic lesion is an acute vasculitis affecting the skin and the conjunctiva. Patients have circulating immune complexes and immunoreactant deposition in the blood vessels of the dermis.

Conjunctiva

The conjunctiva is involved in 90% of cases of Stevens-Johnson syndrome. The severity of involvement parallels that of lesions elsewhere, varying from papillary conjunctivitis, conjunctival pseudomembranes, mild hyperaemia to marked bulla formation and ulceration.

Secondary infection may occur as a result of ruptured conjunctival bullae.

Healing may be accompanied by conjunctival fibrosis and keratinization, symblepharon formation, metaplastic eyelashes which are very fine and arise from the openings of damaged meibomian glands, lacrimal dysfunction in the form of epiphora caused by lacrimal drainage obstruction and, rarely, dry eye from involvement of the lacrimal ductules. These will lead to corneal opacification and vascularization with loss of vision.

CONCLUSION

Malaria is the most important of the parasitic diseases of humans. While it is estimated that 2 million people die every year from malaria in sub-Saharan Africa alone, it has also been observed that malaria can result in visual loss, which can be sudden or gradual.

Chloroquine, which is the commonest drug used for the treatment of malaria, also has deleterious effects on vision if taken for a long time and in large quantities. It is, therefore, recommended that the eye should be frequently evaluated during the management of malaria, especially when it is severe.

References

1. History of Malaria. Royal Perth Hospital, Australia. 1998-2002. www.rph.wa.gov.au/labs/haem/malaria/ index. html.
2. White NJ, Breman JG. Malaria. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds). *Harrison's Principle of Internal Medicine.* 13th edition. London: McGraw-Hill, 1994; 887 - 96.
3. Hviid L. Clinical disease, immunity and protection against *Plasmodium falciparum* malaria in populations living in endemic areas. www.ermm.cbcu.cam.ac.uk.
4. Poncet F. De la retino choroidite. *Palustre Ann d'oculistique* 1879; 79: 201-18.
5. Lewallen S, Taylor TE, Molyneux ME, Wills BA, Courtright P. Ocular fundus findings in Malawian children with cerebral malaria. *Ophthalmology* 1993; 100(6): 857-61.
6. Lewallen S, Bakker H, Taylor TE, Wills BA. Retinal findings predictive of outcome in cerebral malaria. *Trans R Soc Trop Med Hyg* 1996; 90(2): 144-6.
7. Looareesuwan S, Warrell DA, White NJ. et al. Retinal haemorrhage: A common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 1983; 324: 911-15.
8. Haskett P. Retinal haemorrhage in Zambian children with cerebral malaria. *J Trop Ped* 1991; 37: 86-7.
9. Kayembe D, Maertens K, Laey JJ. Ocular complications of cerebral malaria. *Bulletin de la Société Belge d'Ophthalmologie* (Geny) 1980; 190: 53-60.
10. Lucas AO, Gilles HM. *A Short Textbook of Preventive Medicine for the Tropics.* 2nd edition. London: Hodder and Stoughton, 1984; 161-227.
11. Griffin GE, Sissons JGP, Chiodini PL, MitchellI DM. Diseases due to infection - Malaria. In: Haslett C, Chilvers ER, Hunter JAA, Boon NA (eds). *Davidson's Principle and practice of Medicine.* 18th edition. London: Churchill Livingstone, 1999; 148 -64.
12. Garnham PC. Malaria parasites of man: Life cycles and morphology (excluding ultrastructure) in malaria. In: Wernsdorfer WH, McGregor I. (eds). *Principles and Practice of Malariology.* Edinburgh: Churchill Livingstone, 1988: 61-96.
13. Laboratory Diagnosis. Royal Perth Hospital, Australia. 1998-2002. www.rph.wa.gov.au/labs/haem/malaria/ index.html.
14. Lines J, Armstrong JRM. For a few parasites more: Innoculum size, vector control and strain-specific immunity to malaria. *Parasitology Today* 1992; 8: 381-3.
15. Contamin HT. Different genetic characteristics of *Plasmodium falciparum* isolates collected during successive clinical malaria episodes in Senegalese children. *Am J Trop Med Hyg* 1996; 54: 632-643.
16. Baird JK. Age-dependent acquired protection against *Plasmodium falciparum* in people having two years exposure to hyperendemic malaria. *Am J Trop Med Hyg* 1991; 45: 65-76.
17. Breman JG, Steketee RW. Malaria. In: Last JM, Wallace RB (eds). *Maxcy-Rosenau - Last Public Health and Preventive Medicine.* 13th edition. Norwalk: Appleton and Lange, 1992; 240-253.
18. Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bulletin of World Health Organisation* 1983; 61: 1005-16.
19. McGregor IA. Thoughts on malaria in pregnancy with consideration of some factors which influence remedial strategies. *Parasitolia* 1987; 29: 153 - 63.
20. Patel DN, Pradeep P, Surti MM, Agarwal SB. Clinical manifestations of complicated malaria - An overview. *JIACM* 2003; 4(4): 323-31.
21. *Basic and Clinical Science Course.* Section 8: External disease and cornea. 2001-2002: 89-90.
22. Asbury AK, Hauser SL. Guillain-Barre syndrome and other immune-mediated neuropathies. In: Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds). *Harrison's Principles of Internal Medicine.* 15th ed. San Francisco: McGraw-Hill, 2001; 2507-8.
23. Huang X, Aguilar L, Anbuman, P. Burkitt's lymphoma http:www.emedicine.com/med/topic256.htm.
24. Beal MF, Hauser SL. Common disorders of the cranial nerves. In: Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds). *Harrison's Principles of Internal Medicine.* 15th edition. San Francisco: McGraw-Hill, 2001; 2422-3.
25. *Basic and Clinical Science Course.* Section 9: Intraocular inflammation and uveitis. 2001-2002; 78.
26. Kochar DK, Shubhakaran BL, Kumawal I, Thanvi AJ, Vyas SP. Ophthalmoscopic abnormalities in adults with falciparum malaria. *QJM* 1998; 91: 845-52.
27. Hero M, Harding SP, Riva CE, Winstanley PA, Peshu N, Marsh K. Photographic and angiographic characterization of the retina of Kenyan children with severe malaria. *Arch Ophthalmol* 1997; 115: 997-1003.
28. Lewallen S, Harding SP, Ajewole J et al. A review of the spectrum of clinical ocular fundus findings in *P. falciparum* malaria in African children with a proposed classification and grading system. *Trans R Soc Trop Med Hyg* 1999; 93: 619-622.

29. Beare NA, Southern C, Kayira K, Taylor TE, Harding SP. Visual outcomes in children in Malawi following retinopathy of severe malaria. *Br J Ophthalmol* 2004; 88: 321-4.
30. White VA, Lewallen S, Beare N, Kayira K, Carr RA, Taylor TE. Correlation of retinal haemorrhages in children dying of cerebral malaria in Malawi. *Trans R Soc Trop Med Hyg* 2001; 95: 618-21.
31. *Basic and Clinical Science Course.* Section 8: External disease and cornea 2001-2002; 116- 8.
32. Roque MR, Foster CS. Chloroquine/hydroxychloroquine toxicity http://www.emedicine.com/oph/topic245.htm.
33. Kanski J.J. *Clinical Ophthalmology.* 3rd ed. Oxford: Butterworth-Heinemann, 1994; 88- 9.