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Review Article

Beyond COVID-19, the Possible Impact on Eye Health

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Received: May 02, 2020; **Published:** June 19, 2020

Abstract

The disease, COVID-19 has brought a lot of untold hardships to people, affecting persons from all cadres of human existence and causing a great deal of tragedy to nations. The race to halt this unseen enemy has gained momentum. This is seen in many trials, which are currently re-evaluating existing drugs and possibly new ones aimed at stopping this global pandemic. One of the alternative drugs which has been repurposed is an antimalarial known as chloroquine and its analogue-hydroxychloroquine. This drug with its analogue has documented side effects with prolonged use, increased dosage and in persons with renal failure, with effects especially on the eyes which can even lead to irreversible blindness. What then could be the possible impact of this drug on those receiving this type of treatment during the course of their therapy for COVID-19?

Keywords: *COVID-19; Hydroxychloroquine; Chloroquine*

Introduction

In current times, the media has been awash with the news of the rapidly virulent virus which has engulfed the whole world. From emerging economies to established economies, it has dealt a blow. The world has been hit by an unseen enemy, the Covid-19 disease which according to research is caused by a novel virus known to cause severe acute respiratory syndrome coronavirus 2 (SARS-COV 2). This condition which initially originated in Wuhan in China, further spread uncontrollably engulfing the whole world causing untold harm, hardship and fatalities globally [1,2]. Hospitals especially in hotspots or epicentres of infection like Italy, Spain, New York were in no way prepared enough, as no health care system anywhere in the world was prepared for this tragedy. Different measures had to be taken to expand care. These included converting places like stadia, conference centres, even parks to temporary hospitals just to accommodate the increasing number of cases as there are marked shortages both in hospital spaces, health care workers and even personal protective equipment needed for work [3]. The upward trend or the spike in cases and death has even overshot the projections of modellers in prediction of expected numbers of infections and deaths. Reported cases have well passed the one million mark, with numbers steadily rising. However, experts predict that the unreported cases may be as high as six times the number of reported cases [4]. This is why many countries are ramping up their testing capacity.

In this race to mitigate the harm caused by this deadly condition which continues to strike all persons from all walks of life [5], a lot of different strategies have been employed. Awareness campaigns have been initiated by government and many other agencies, to sensitize the public on the importance of continuous hand washing [6], the use of hand sanitizers, avoidance of facial and orifical touch, use of masks and hand gloves where necessary, practicing of social distancing, also referred to as "physical distancing", the avoidance of crowded places and isolation- both self and hospital based.

However, many trials [7] have been started and many options for treatment [8] advocated for persons at different stages of the disease [7,9]. Also concerted efforts are being made to find a vaccine which can even prevent the infection from taking place. One which is outstanding in all of this is the use of antimalarials in the treatment of Covid 19 patients[10] These antimalarials like chloroquine and hydroxychloroquine have been repurposed to help contain this disease, although some early researches [11] suggest that in addition to its antimalarial effect [12], it might also have some antiviral effects [11,13].

The side effects especially of chloroquine which is well documented both on the eyes and other organs, at this point in time, pales into insignificance when compared to how virulent this virus is. In fact, world leaders like the US president Donald Trump had given his approval even though there is paucity of data on the efficacy of this drug as time is of essence in this race to save lives against all odds; the ultimate goal being to save lives despite the cost. Nonetheless, experimental studies have shown that it could work experimentally (Figure 1) but when introduced into the human system, proves otherwise as it may cause a great deal of harm [10]. However, information emerging from China suggests that the chloroquine drug therapy might be effective against COVID-19 [14,15]. The fact, then remains that this emerging infection which until recently was unknown has no previous data or information about it. What is currently known is based on the observation following the trends and experiences of countries like China where the initial outbreak was recorded. However new information unfolds on a daily basis as countries continue to learn from their sometimes tragic experiences.

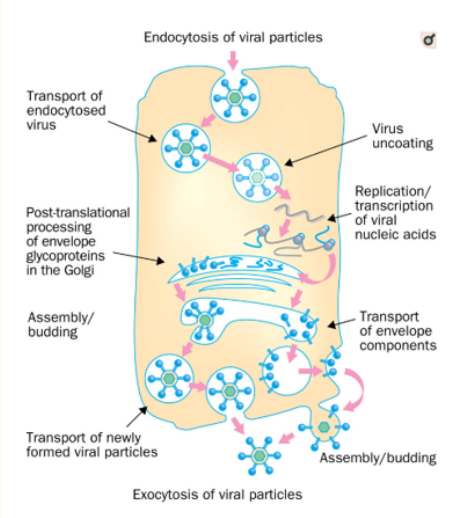

Figure 1: *Virus breakdown by chloroquine (marked by purple arrows) [12].*

It is well known that the use of quinine comes with a lot side effect especially when used for a long time. What is the drug regimen - the dosage of the drug, frequency and duration? Is dosing individualised based on symptoms severity? Is the patient's comorbidities such as heart diseases considered for possible drug interaction? What is the possible effect on the vulnerable such as older persons who are more susceptible to the virus, as shown by available data? How is affected individuals' susceptibility to be gauged if they had never taken chloroquine or its analogue prior to this outbreak? What hyper allergic reactions are to be expected? What of the younger persons and the middle aged persons too? What will be the impact of this treatment on eye health?

Although Covid-19 hit the world unexpectedly, viral infections are not new to medical pathology. Prominent antiviral drugs have been used over time to combat both systemic and ocular viral infections. Like Covid-19, viral infections significantly manifest high mortality

and morbidity among immunosuppressed individuals [16]. Hence, the unrelenting research in the development of drugs that would be potent and safer [17].

Besides ongoing clinical trials on chloroquine in treating Covid 19, some known antiviral drugs are also on trial including the antiretroviral drugs used in HIV patients [18]. Researches have shown relationships' between some antiviral drugs and varying forms of retinopathies in the eye as in the case of treatment of hepatitis C using interferon-alpha and ribavirin [19]; immune recovery uveitis secondary to Highly active antiretroviral therapy (HAART) [20] as well as ocular syphilis among patients receiving HAART [21]. With these relationships of ocular toxicity associated with therapies in management of viral infections, it is important that researchers in eye care be alerted to the possible toxicity that may arise from the management of covid 19, whether an antiviral drug or chloroquine is used.

Chloroquine and the eyes

The known forms of chloroquine and its analogue which is currently available are chloroquine sulphate (Nivaquine; Rhone Poulenc, Paris, France), chloroquine phosphate (Aralen; Sanofi-Synthelabo, New York, NY, USA) and hydroxychloroquine sulfate (Plaquenil, Sanofi-Synthelabo) [22]. Chloroquine (Nivaquine, Avlocor) and hydroxychloroquine (Plaquenil) are quinolone antimalarial drugs used in the prophylaxis and treatment of malaria as well as in the treatment of certain rheumatological disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus and has also been advocated in the treatment of calcium abnormalities associated with sarcoidosis [23]. However certain side effects such as quinine amblyopia could occur even with small doses of the drug in susceptible individuals. Patients may develop near total blindness, deafness and tinnitus. In the eyes, the pupils are fixed and dilated. Fundus examination reveals retinal oedema, marked pallor of the disc and extreme attenuation of retinal vessels. "Visual fields are markedly contracted" [24].

Chloroquine causes retinal problems with prolonged use. Adverse effects are infrequent at doses for malaria prophylaxis and treatment but are more common with higher or prolonged doses given for resistant malaria or for rheumatoid arthritis or lupus erythematosus. Corneal deposits of chloroquine may be asymptomatic or may cause halos around lights or photophobia. These are not a threat to vision and reverse when the drug is stopped. Retinal toxicity is more serious and may be irreversible. In the early stage it takes the form of visual field defects; late retinopathy classically gives the picture of macular pigmentation surrounded by a ring of pigment -the 'bull's-eye' macula (Figure 2). The functional defect can take the form of scotomas, photophobia, defective colour vision and decreased visual acuity resulting, in the extreme case, in blindness [23].

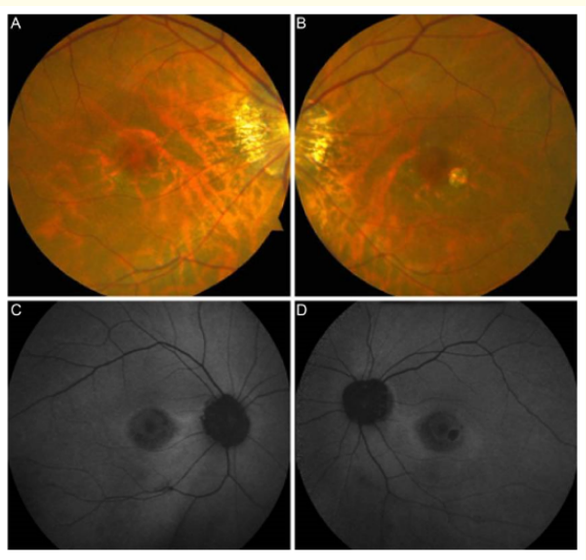

Figure 2: *Photographs of the right (A) and left (B) eyes. Fundus autofluorescent (FAF) images of the right (C) and left (D) eyes are also shown. The FAF image shows a hypofluorescent lesion in the foveal and perifoveal areas consistent with bull's eye retinopathy. A prominent hypofluorescent lesion is visible in the left eye, indicating a marked atrophy of the retinal pigment epithelium layer. The bull's eye pattern of depigmentation is also evident on fundus photography and fundus autofluorescent images [25].*

Other reactions include pruritus, which may be intolerable and is common in Africans, headaches, gastrointestinal disturbance, precipitation of acute intermittent porphyria in susceptible individuals, mental disturbances and interference with cardiac rhythm, the latter especially if the drug is given i.v. in high dose (it has a quinidine-like action). Long-term use is associated with reversible bleaching of the hair and pigmentation of the hard palate [26].

Chloroquine retinotoxicity is related to the total cumulative dose. The normal daily dose is 250 mg: a cumulative dose of less than 100 mg or treatment duration under 1 year is rarely associated with retinal damage. The risk of toxicity increases significantly when the cumulative dose exceeds 300g daily for 3 years. However, there have been reports of patients receiving cumulative doses exceeding 1000g who did not develop retinotoxicity. If possible, chloroquine should be used only if other agents are ineffective [27].

Hydroxychloroquine is much safer and less toxic than chloroquine and if the daily dose does not exceed 400 mg the risk of retinotoxicity is negligible. The risk of toxicity however, is increased if a daily dose over 6.5 mg/kg is administered for longer than 5 years, although even then the risk is still very small. This drug has been used in different capacities: oncology, in paediatrics, in rheumatological and dermatological disorders, in addition to its use as an anti-malarial drug [25]. In all cases, risk increases with prolonged use, prolonged doses and a reduced renal function in the patients.

Higher doses of chloroquine may cause nausea, vomiting, diarrhoea, rashes, pruritus and rarely psychoses. Prolonged use may cause irreversible retinal damage. Other adverse effects of quinine are abdominal pain, tinnitus, headache, blindness and hypersentivity reactions [27]. Will this form of treatment then be used on patients who have comorbidities such as heart diseases, known kidney problems and the like? Hopefully not. Other forms of treatment which appear safer for this class of patients most likely should be used for them.

The question now arises, how long does the corona virus live in the human body before an outcome (death or recovery), with or without therapy? The available information shows that this is dependent on the severity of the disease condition in an individual. This varies from mild to severe. In mild cases recovery occurs within 2 weeks whereas severe cases may need 4 - 6 weeks [28]. This then suggests that the use of these antimalarials if only for this short time may not produce the adverse reactions for which they are known for, unless the individuals whom they are administered to are susceptible to them, then that becomes another problem. However anecdotal evidence shows that older persons who have tested negative to the virus and have been discharged, may not be fully recovered but may battle and live with the impact for the rest of their lives. In fact current data from South Korea shows that there is the possibility of reinfection to those who had suffered from the Corona virus infection, recovered and had tested negative [29]. If this is so, then are we going to be seeing an increased prevalence of retinal diseases when this pandemic subsides? The answer to this question currently appears vague. But what we do know is that the lessons and damages caused by this pandemic leave a scar that will not be forgotten in a hurry. The effects will be here with us for a long time. As time unfolds, we will fully understand the manifestations and implications of the problems it has left in its trail. Finally, whatever the impact and disabilities it has wrought, they will be managed. Humans are known to be amazingly resilient even in tough times as the present situation shows.

Conclusion

From systemic conditions like hypertension and diabetes to drugs including chloroquine, research has continually unravelled how the eye is often affected by other activities in the human body. Considering the importance of vision to daily life, it is of necessity that researches keep looking out for possible side effects of drugs especially as morbidities are abounding in our society. As more drug options are explored in the management and treatment of COVID-19, their effects on the tissues of the eyes should be intentionally studied and possible precautions also published.

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Volume 11 Issue 7 July 2020