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## Acute Blindness in a Child after Quinine treatment for Severe Malaria

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### Abstract

Although blurred vision from quinine toxicity is well documented in literature, an acute effect leading to blindness is infrequently reported. We report a case of sudden bilateral blindness in a child after quinine treatment for severe malaria. Ocular examination revealed no acute pathology except widely dilated non-reactive pupils. The site within the retina of the toxic effect of quinine remains controversial. Literature on proposed mechanisms is reviewed in this article. This case highlights the potential toxic effects of quinine in children and the lack of a characteristic fundi appearance.

**Keywords:** Plasmodium; Falciparum; Severe malaria; Quinine blindness

### Introduction

Malaria remains a major public health problem globally. It is estimated that each year there are about 350–500 million clinical cases of malaria, which result in more than 1 million deaths [1]. About 80% of these deaths occur in children under five years old that live in areas of intense malaria transmission, notably in sub-Saharan Africa [1,2]. The most severe form of malaria otherwise called cerebral malaria is caused by resistant *Plasmodium falciparum* infections and constitutes about 95% of all malaria cases reported to health care facilities in Ghana [3]. The treatment requires prompt, safe, and effective intravenous anti-malarial drugs. The WHO recommends that people with severe malaria be given an initial dose also referred to as the loading dose, of 20 mg salt/kg of the dihydrochloride salt infused at constant rate over 4 hours, followed by 10 mg/kg of the salt infused over 2 hours, and repeated every 8 hours [4]. This is followed by quinine maintenance doses [4,5]. The rationale for the loading dose is the urgent need to achieve an effective quinine concentration in the blood to prevent patient from dying as death in severe malaria often occurs in the first to 48 hours of admission to hospital or clinic [6].

Quinine, a naturally occurring alkaloid originally used for the treatment of muscle cramps, is now most commonly used for the treatment of malaria. Visual loss is one of the most common effects documented in literature, but the exact site within the retina of the toxic effect remains a subject of controversy. Other adverse reactions including hearing loss and hypotension are also well reported with quinine intoxication and some of these have been noted in context of therapeutic dosages [7-10]. The mean time of onset of blurred vision is 6 to 15 hours, while usually gradual, can be sudden. It may last up to 10 weeks or longer. Generally there is full recovery in 1 to 3 weeks; however patient may become permanently blind [11]. Ophthalmic findings during the acute phase are dilated pupils and unresponsiveness to light in proportion to the degree of blindness [7-10]. The ophthalmoscopic appearances have varied considerably from case to case and this has occasioned much dispute concerning the mechanism by which vision is affected. In some cases the retinal vessels have appeared narrowed early [11]. In another group of cases the retina has appeared oedematous and the papilla hyperaemic [9]. In yet other cases the fundi have appeared normal at an early stage while the patient was already profoundly blind [8,10]. It has been reported very frequently that at a later stage, after some days or weeks, the retinal arterioles have become strikingly narrowed, often at a time when central vision had returned,

or was returning [7,8]. Pallor of the optic nerve heads has often been noted, developing gradually, generally proportional to the amount of permanent loss of visual field [9]. In the acute stages of loss of vision, the electroretinogram may be normal. Thereafter it becomes abnormal during the phase of visual improvement and parallels the changes of visual acuity on the second or third day. Visual evoked potentials, dark adaptation, and color testing measurements are often abnormal [9].

### Case Report

A one year 6 months old male child presented to the emergency unit of Effia Nkwanta Regional Hospital, with a 4 days history of fever, vomiting and a day history of convulsion. The initial physical assessment showed an ill looking child, febrile, anicteric and twitching. The liver was 4 cm enlarged and the spleen was just a tip felt on the left hypocondrium. Child was semi-conscious with an inappropriate response to pain. A presumptive diagnosis of severe malaria was made and child was subsequently admitted to children's ward of the hospital. Medications prior to admission included quinine 90 mg 8 hourly (10 mg/kg), intramuscular injections for the first 24 hours and syrup quinine for 6 days. Intravenous infusion of dextrose saline 500 mls over 24 hours at 8 drops per minute was given together with the intramuscular quinine to prevent hypoglycemia. Other drugs given were intravenous 500 mg ceftriazone daily for 72 hours, syrup paracetamol and intravenous diazepam.

Admission laboratory test results revealed the following levels: hemoglobin 4.3 g/dl; WBC 25.8; platelet 320; MP+. The clinical features and the history suggested a diagnosis of severe malaria that was confirmed by a positive thick blood smear for *Plasmodium falciparum*. Child was transfused 180 mls of pack cells and placed on the malaria treatment. Post transfusion HB was 6.0 g/dl. The malaria was successfully treated and child was subsequently discharged 5 days after admission, feeling better and well. Child came for the mandatory

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2 weekly review and the mother complained that few days after being discharged she noticed that the child was bumping into things at home.

At the casualty, a toy was placed in child's view and there was no concentration of the child to the toy. Child was transferred to an eye clinic for comprehensive eye examination. Upon examining his eyes, his pupils were fully dilated and un-reactive. Ophthalmoscopic examination revealed no acute pathology. Both fundi were unremarkable and there were no evidence of macular or retinal edema or ischemia. Child was referred to an ophthalmologist and subsequently lost to follow up.

## Comments

This child had the typical ocular changes of acute quinine toxicity. Although he was given a combination of quinine and other drugs (dextrose saline, ceftriazone, paracetamol and diazepam) no visual toxicity has been associated with any of the other drugs. The mother reported noticing that the child was bumping into things at home few days after child's discharge from the hospital, though it is conceivable that the visual loss may have started before the mother noticed it. Visual loss from quinine toxicity can start as early as 6 hours after ingestion and has been associated with quinine serum peak concentrations above 10 ug/ml [11]. The patient may experience sudden blurred vision progressing to flickering vision and disturbances in color perception, often followed by decreasing visual fields which sometimes progresses to complete blindness after 15 hours [9]. The sudden visual loss was at first believed to be caused by retinal arterial constriction causing inner retinal ischemia and eventually optic atrophy [8]. However, early fundoscopic examinations of patients with quinine toxicity and visual changes have shown normal fundus and arteriolar caliber as in this child's case, and this has occasioned much dispute concerning the mechanism by which vision is affected. Fundoscopic changes appear to be seen only when vision is improving suggesting a direct toxic effect to the neuroretina layers [12]. In this direction, several plausible biological mechanisms have been proposed to explain its ocular toxic effect. Electroretinographic changes suggest quinine directly affects the photoreceptor and ganglion cell layers [9]. If this is so, acetylcholine is most likely to be affected, for several reasons:

1. The inner synaptic layer of the retina, where quinine may be acting, have stained heavily for acetylcholinesterase in a previous study [13], indicating that acetylcholine is present in the layer.

2. Quinine has a curare-like action on neuromuscular junctions [14] which includes an anticholinergic action such as mydriasis. Ganglion cells are thought to be cholinoreceptive neurones, Quinine, with its known curare-like action, may act here.

3. A sub-population of amacrine cells also probably synthesises acetylcholine as a neurotransmitter [15]. Quinine again may block this action.

The child's pupils were widely dilated and un-reactive. Pupillary dilatation is a consistent feature of quinine toxicity [7-10]. The effect may be due to either a neurological efferent pathway defect or local sphincter paralysis and may lead to damage of the parasympathetic nerve supplying the iris, to the neuromuscular junction, or to the sphincter papillae itself [8,9]. In some patients the pupillary changes may be so extreme that the patient is left with dilated atrophic pupils [9].

It is likely that our patient was highly susceptible to quinine or was overdosed given that a number of case reports have described irreversible retinal and neurological abnormalities associated with very high levels of quinine in blood [9,10]. Though the peak serum quinine

concentration was not taken for this case but at the therapeutic dose used, no evidence of ocular quinine toxicity was found in a study in Malawi [16]. However, another study showed transient loss of vision in an average person with a dose lower than that administered on our patient [17]. There seems to be a definite idiosyncrasy to quinine, so that some people can stand large amounts, whereas others will show marked symptoms with relatively small doses. This finding underscores the need to test individuals for susceptibility before administration.

## Treatment

Treatment of quinine toxicity is supportive therapy. There are several suggested treatments aimed at reducing the serum quinine level or at preventing or reversing retinal vessel spasm but the most commonly used is stellate ganglion block [18]; others which may be of benefit are vasodilators, and adrenocorticotrophic hormone. However, all these require rapid referral, as treatment is unlikely to be successful more than 24 hours after ingestion. The prognosis for the majority of patients with quinine ocular toxicity is good, as most affected patients have a return of vision within hours to days of exposure, although there is usually residual constriction of the visual field and frequently only a small central island of vision returns [19]. Visual recovery has been reported in cases without any treatment [20,21].

## Conclusion

Quinine toxicity should be suspected in patients with sudden bilateral visual loss and widely dilated non-reactive pupils in the absence of any ophthalmic finding. Rapid referral and prompt treatment is advised.

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