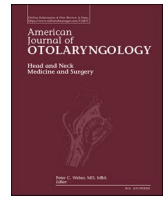


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Chloroquine and hydroxychloroquine ototoxicity; potential implications for SARS-CoV-2 treatment. A brief review of the literature

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ABSTRACT

Introduction: Current clinical evidences do not support any specific treatment against SARS-CoV-2. Chloroquine (CQ) and hydroxychloroquine (HCQ) are typically used in the treatment of rheumatoid arthritis, systemic lupus erythematosus and malaria; they have been considered for off-label and compassionate use in several countries against moderate to severe cases of COVID-19 and there’s actually a massive demand of these two drugs. The aim of this paper is to briefly review the published literature, summarizing evidences about audiological implications after CQ and HCQ treatment.

Methods: We conducted a review of the literature on Medline and Pubmed platforms from 27th May 2020 to 30 May 2020. We combined MeSH terms of “chloroquine”, “hydroxychloroquine”, “ototoxicity”, “hearing loss”, “tinnitus”, “deafness” and “hearing”. Publications with relevant data were included. Selected data (authors, country and year; sample size; study design; audiological side effects) were extracted and summarized in a table.

Results: Of 45 initial studies, 14 met inclusion criteria. The authors found six cases of HCQ ototoxicity; Tinnitus was reported in 2 cases, and it was found to be reversible or irreversible. Sensorineural hearing loss after HCQ use was reported in 7 patients; it was found to be irreversible or partially reversible after discontinuation of HCQ in 6 cases. Eight papers reporting CQ ototoxicity were; tinnitus was not reported by any authors. Sensorineural hearing loss after taking CQ was reported in 6 patients; it was found to be irreversible after discontinuation of CQ in 5 patients. One patient showed abnormal gait after a single intramuscular injection of CQ. Thirteen patients’ Auditory Brainstem Response (ABR) were found to be abnormal, but they resolved after CQ discontinuation.

Conclusions: CQ and HCQ related ototoxicity is widely reported in the literature although the pathophysiological mechanism is not well known. Current data are not sufficient enough to support the use of CQ and HCQ as therapy for COVID-19, but considering the growing demand for these two drugs and the number of people around the world who have taken and will take CQ and HCQ, it must necessarily consider the clinical and social impact of long term audiological side effects.

1. Introduction

The Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2), also known as COVID-19 pandemic, is engaging clinicians around the world in an unprecedented effort and is forcing the resilience of healthcare systems [1]. Current clinical evidences do not support any

specific treatment against SARS-CoV-2 [2,3].

Chloroquine (CQ) and hydroxychloroquine (HCQ), quinine-related compounds, are typically used in the treatment of rheumatoid arthritis, systemic lupus erythematosus and malaria; they have been considered for off-label and compassionate use in several countries against moderate to severe cases of COVID-19 and there’s actually a

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Table 1
Hydroxychloroquine ototoxicity.

Author, country, year	Sample size	Age, y/ gender	Disease	Study design and dosage of Hydroxychloroquine (HQ)	Results
Seckin et al, Turkey, 2000	1	34 yr/Male	Rheumatoid arthritis	Case report; 400 mg/day	After six months of combination therapy, he developed tinnitus and bilateral mild sensorineural hearing loss. Tinnitus vanished two weeks after withdrawal of HQ; two months lateral symptoms of hearing loss had improved (the follow-up audiogram was normal)
Khalili et al, Iran, 2014	1	57 yr/Male	Rheumatoid arthritis in HIV+	Case report; 200 mg/day	Bilateral moderate to severe sensorineural hearing loss one months after HQ; two months after discontinuation of HQ, the follow-up audiogram showed mild to moderate sensorineural hearing loss
Fernandes et al, Brazil, 2018	1	51 yr/ Female	Systemic lupus erythematosus	Case report; 400 mg/day	Three years after use of HQ she complained tinnitus and moderate SNHL on left ear and mild to moderate on right ear. This condition persisted after discontinuation of HQ
Coutinho and Duarte, Portugal, 2001	1	7 yr/ Female	Idiopathic pulmonary haemosiderosis	Case report; 200 mg/day	She had progressive hearing loss in the right ear two years after sustained HQ use. Auditory Brainstem Response test showed no response at 90 dB in the right ear
Lim and Tang, Malaysia, 2011	1	11 yr/ Female	Systemic lupus erythematosus	Case report; 100 mg/daily	Bilateral low-frequencies hearing loss two months after HQ use.
Johansen and Gran, Norway, 1998	2	44 yr/1 Male, 1 Female	Systemic lupus erythematosus	Data not available	Irreversible sensorineural hearing loss several years after HQ use

Table 2
Chloroquine ototoxicity.

Author, country, year	Sample size	Age, y/ gender	Disease	Study design and dosage of Hydroxychloroquine (HQ)	Results
Mukherjee and Enugu, Nigeria, 1979	1	6 yr/Female	Malaria	Case report; 250 IM mg/day × 7 days	Severe unilateral hearing loss, improved after prednisolone injection
Matz and Naunton, United States, 1968	1	7 yr/Male	The mother took chloroquine, during the first trimester of pregnancy for Systemic Lupus Erythematosus. The boy died from an epithelial ependymoma of the right cerebellum	Case report; 250 mg/day	Profound sensorineural hearing loss. Post-mortem inner ear examination showed complete absence of the inner and outer hair cells throughout all of the turns of the cochlea
Hart and Naunton, United States, 1963	2	5 yr/Male, 3 yr/Male	The mother took chloroquine during both pregnancies	Case reports; 250 mg/day	Severe bilateral cochleovestibular paresis
Hadi et al, United States, 1995	1	2.5 yr/Male	Malaria	Case report; 65 mg (single IM therapeutic dose)	Abnormal gait few our after chloroquine injection; hearing loss on 2nd day. Persistent hearing loss three and five years after chloroquine injection
Dwivedi and Mehra, India, 1978	1	52 yr/Male	Malaria	Case report; 1000 mg os	Bilateral permanent and profound deafness 1.5 h after taking chloroquine
Bortoli and Santiago, Brazil, 2007	/	/	/	Review of the literature	Sensorineural hearing loss and tinnitus were described as side effects after taking chloroquine
Borba et al, Brazil, 2004	9	Data not available	Mothers took chloroquine during first trimester of pregnancy	Case-control study, 250 mg/day	No significant difference in hearing threshold by pure tone audiometry of children between exposure group and control (non-exposure) group
Bernard, Canada, 1985	74	From 18 to 50 yr (39 yr median)	70 case of Rheumatoid Arthritis and 4 cases of Systemic Lupus Erythematosus	Observational study; 205 mg/day	No hearing change in pure tone audiometry. Thirteen case of abnormal ABR, resolved after discontinuation of chloroquine

massive demand of these two drugs.

Several studies indicated that CQ and HCQ show antagonism against COVID-19 in vitro [4]; there are actually over 70 clinical trials that have shown poor evidences regarding the effects of these drugs in patients.

Commons side effects of CQ and HCQ reported in literature are hearth rhythm problems, liver and kidney problems, hypoglycaemia, retinopathy, muscle weakness [5]. The literature also contains case reports of ototoxicity (hearing loss, tinnitus) due to the damage of inner ear structures [6].

The aim of this paper is to briefly review the published literature, summarizing evidences about audiological implications after CQ and HCQ treatment, and draw conclusions about potential implications in COVID-19 patients treated with CQ and HCQ.

2. Methods

We conducted a review of the literature on Medline and Pubmed platforms from 27th May 2020 to 30 May 2020. We combined MeSH terms of “chloroquine”, “hydroxychloroquine”, “ototoxicity”, “hearing loss”, “tinnitus”, “deafness” and “hearing”. Publications with relevant data were included. Selected data (authors, country and year; sample size; study design; audiological side effects) were extracted and summarized in a table.

3. Results

3.1. Hydroxychloroquine ototoxicity

Six cases of HCQ ototoxicity, from 1998 to 2018, were identified and summarized in Table 1. Tinnitus was reported in 2 cases [7,8], and it was found to be reversible [7] or irreversible [8]. Sensorineural hearing loss after HCQ use was reported in 7 patients (three males, four females; five adults, two children) [7–12]; the onset of hearing loss after HCQ treatment varied from 1 month [9] to several years [8,10,12]. It was found to be irreversible or partially reversible after discontinuation of HCQ in 6 cases [8–12]. Systemic Lupus Erythematosus (three patients) [8,11,12] and Rheumatoid Arthritis (two patients) [7,9] were the most common diseases for which patients took HCQ.

3.2. Chloroquine ototoxicity

Eight papers, from 1963 to 2007, reporting CQ ototoxicity were identified and summarized in Table 2. The comprehensive sample size of the works was 91 patients; there were 5 case reports [13–17], 1 case-control study [18], 1 review article [19], 1 observational study [20].

Tinnitus was not reported by any authors. Sensorineural hearing loss after taking CQ was reported in 6 patients (five males, one female; one adult, five children) [13–17,19]. It was found to be irreversible after discontinuation of CQ in 5 patients [13,15–17]. One patient showed abnormal gait after a single intra-muscular injection of CQ [17]. Thirteen patients' Auditory Brainstem Response (ABR) were found to be abnormal, but they resolved after CQ discontinuation [20].

4. Discussion

Sensorineural hearing loss, tinnitus and balance involvement are possible side effects of CQ and HCQ, as reported in medical literature; in addition, the use of these drugs can worsen prior hearing loss.

CQ and HCQ are commonly used against malaria (10 mg/kg at the beginning, then 5 mg/kg after 6–24–48 h) [21] and some autoimmune diseases as systemic lupus erythematosus or rheumatoid arthritis (400 or 600 mg/day); we should consider other possible causes of hearing loss, as the autoimmunity itself.

The exact mechanism of CQ and HCQ related ototoxicity is not well established; it is probably related to the destruction of stereocilia and the reduction of the neutron population; therefore, quinine-related compounds showed a long-term retention in melanocytes of inner ear, and this could explain the late onset of lesions and symptoms.

Hennebert and Fernandez [22] demonstrated that the quinine injected into the middle ear of guinea pigs produced signs of temporary unilateral labyrinthectomy; hair cells, limbus, and stria vascularis were the most involved inner ear structures, particularly near the round window. In addition, Gradenigo [23] and Wittmaack et al. [24] suggested the possibility of vasoconstriction for ototoxicity.

Most of the literature on this topic is not recent; therefore, there are only case reports and a few observational studies. Larger study with rigorous methodology should be needed to obtain reliable data about audiological implications.

Several registered clinical trials are being conducted to assess the effectiveness of CQ and HCQ against COVID-19 pandemic; the dose of CQ used in these trials is higher than dosage of CQ reported for malaria treatment [25]. Most authors suggested a total dosage of 1 g daily for 10 days for the treatment of SARS-CoV-2. In addition, the duration of treatment against SARS-CoV-2 is substantially shorter than treatment period in patients with chronic autoimmune disease (months or even years).

No ototoxicity or cochleovestibular side effects are described in recent trials, but we should also consider two issues: 1) otological side effects often appear at a distant of months or years from CQ or HCQ discontinuation (especially HCQ ototoxicity), and 2) should be

separately assessed the role of the other drugs used in treatment protocols with CQ and HCQ.

The use of CQ and HCQ during pregnancy has remained controversial for a long time. It is generally considered safe in pregnant women [26] but it should be administered with caution in the first trimester of pregnancy because it can lead to cochleovestibular abnormalities in newborns [15].

Costedoat-Chalumeau et al. [27] concluded that HCQ can be maintained throughout pregnancy in patients with systemic lupus erythematosus. In Zhou et al. opinion's HCQ showed less side effects than CQ due to its safer profile in pregnancy [28]; this point is also confirmed by Zhao et al. [29]. A recent work by Lacroix et al. [30] didn't report any otological abnormalities in newborns; therefore they recommend to remember to a woman who took HCQ or CQ that she will remain exposed up to 210 days for CQ and 420 days for HCQ after their discontinuation.

5. Conclusions

CQ and HCQ related ototoxicity is widely reported in the literature although the pathophysiological mechanism is not well known. Current data are not sufficient enough to support the use of CQ and HCQ as therapy for COVID-19, but considering the growing demand for these two drugs and the number of people around the world who have taken and will take CQ and HCQ, it must necessarily consider the clinical and social impact of audiological side effects in the long term.

Pure-tone audiometry evaluation should be assessed in patients treated with CQ or HCQ, especially in patients with a poor hearing function, which could benefit from the use of antioxidant drugs for the protection of cochlear sensory.

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Declaration of competing interest

The authors have no conflict of interest to disclose.

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