

Forgotten Effect of Hydroxychloroquine in the Sjogren's Syndrome: Ototoxicity

Sjögren Sendromu'nda Hidroksiklorokin Unutulan Etkisi: Ototoksisite

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Abstract

Objectives: Sjogren's syndrome is a chronic, autoimmune and inflammatory disease. Sensorineural hearing loss is reported in ear involvement but the cause of this hearing loss is not known yet. Hydroxychloroquine has been long known to have ototoxic effects and it is often used in Sjogren treatment. In our study, we tried to explain the correlation of hearing loss in Sjogren with hydroxychloroquine use.

Materials and Methods: A prospective control study was designed and Sjogren syndrome patients were divided into two. Group 1 consist of 20 patients with drug usage. Group 2 consist of 15 patients without drug usage. Pure tone audiometric examination was done to all patients. Results were analyzed.

Results: There was not any statistically significant difference between the groups for either ear at 250 Hz, 500 Hz, 1000 Hz and 2000 Hz in the audiograph ($p>0.05$). There was a statistically significant difference at 4000 Hz in the left ear and 8000 Hz in the right ear and at 10,000 Hz in both ears ($p<0.05$). There was not any statistical significance at 4000 Hz in the right ear and at 8000 Hz in the left ear ($p>0.05$).

Conclusion: Sensorineural hearing loss can occur particularly at high frequencies in the Sjogren's syndrome. This can be related to the duration of the disease or maybe it can occur due to hydroxychloroquine that is commonly used in treatment and known to be ototoxic. In our study, it was found that this drug had an impact on hearing loss. As the drug can accelerate the hearing loss that is already anticipated, it can also be completely responsible for the hearing loss by itself.

Key Words: Hydroxychloroquine, Ototoxicity, Sjogren

Öz

Amaç: Sjögren sendromu kronik, otoimmün ve enflamatuvar bir hastalıktır. Sensörinöral işitme kaybı kulak tutulumu olarak bilinir, ancak sebebi henüz bilinmemektedir. Hidroksiklorokin uzun süredir Sjögren tedavisinde kullanılmaktadır ve ototoksik etkileri olduğu bilinmektedir. Çalışmamızda Sjögren'deki işitme kaybının hidroksiklorokin kullanımı ile korelasyonu açıklanmaya çalışılmıştır.

Gereç ve Yöntem: Prospektif bir çalışma planlandı ve Sjögren sendromlu hastalar iki gruba ayrıldı. Grup 1, 20 hastadan oluşmaktaydı ve bunlar ilaç tedavisi altında olan hastalardı. Grup 2, 15 hastadan oluşmaktaydı ve henüz hidroksiklorokin kullanmaya başlamamış hastalardan oluşmaktaydı. Tüm hastalara pure tone odyometri incelemesi yapılmış ve sonuçlar değerlendirilmiştir.

Bulgular: Odyografide her iki kulak için 250 Hz, 500 Hz, 1000 Hz ve 2000 Hz'de gruplar arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0,05$). Sol kulakta 4000 Hz'de ve sağ kulakta 8000 Hz'de ve her iki kulakta 10.000 Hz'de anlamlı fark elde edildi ($p>0,05$). Sağda 4000 Hz'de ve solda 8000 Hz'de anlamlı fark elde edilmedi ($p>0,05$).

Sonuç: Sjögren sendromunda özellikle yüksek frekanslarda sensörinöral işitme kaybı görülebilir. İşitme kaybı hastalığın süresi ile ilişkili olabileceği gibi tedavisinde sıklıkla kullanılan ototoksik olduğu bilinen hidroksiklorokin sebebi ile olabilir. Çalışmamızda da ilacın bu hastalıkta işitme üzerinde etkisi olduğu tespit edilmiştir. Tedavide kullanılan ilaç işitme kaybını hızlandırıyor olabilir ya da işitme kaybının tek sebebi de olabilir.

Anahtar Kelimeler: Hidroksiklorokin, Ototoksisite, Sjögren

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Introduction

Sjogren's syndrome is a chronic, autoimmune and inflammatory disease that involves salivary and lacrimal glands leading to dryness in mouth and eye with focal lymphocytic infiltration in these glands. It can occur alone (primary Sjogren's syndrome) or arise in the presence of another autoimmune disease (secondary Sjogren's syndrome). It is usually seen during the fourth and fifth decades of life and its prevalence ranges from 0.5% to 4.8%, with a female/male ratio of 9/1. It is known that it can involve other organs as well besides lacrimal and salivary glands. Although sensorineural hearing loss is reported in ear involvement, the cause of this hearing loss is not known yet (1-6).

Hydroxychloroquine is the most commonly used and preferred drug for treatment of dry eyes and mouth. It has been long known that this drug has ototoxic effects and there are studies supporting this in literature (7-13).

Our purpose in this study is to compare pure tone audiometric findings in patients with Sjogren's syndrome who are newly diagnosed and have not yet started on hydroxychloroquine with those who use hydroxychloroquine, and to evaluate the results, and to be able to establish the place of audiological examinations in early diagnosis of hydroxychloroquine ototoxicity.

Materials And Methods

Fifteen patients with a diagnosis of Sjogren's syndrome who did not receive hydroxychloroquine and twenty patients who received hydroxychloroquine in our tertiary center were included in this study. Audiometric examination was performed to all patients. Prior to the tests, all patients underwent a complete ear nose throat, head and neck examination, those who met the inclusion criteria were included in the study after obtaining an informed consent form. Ethical approval was obtained from Ankara University Medical School Ethical committee (number: 2014-12-21).

Patients with a history of previous otologic surgery, patients who were diagnosed as and followed for hearing loss, patients with a history of other ototoxic drug use, patients who has history of family hearing loss, history of trauma, patients who were under 18 years of age and patients with active infection were excluded.

The study was approved by the ethics committee of our institution and conducted in accordance with ethics principles stated in the Declaration of Helsinki. Written informed consent was obtained from patients who participated in this study.

Audiological Measurements

Pure tone audiometric measurements were performed with AD629 Interacoustics (Denmark, 2012) equipment in sound proof cabins where noise level does not exceed 30 decibel (dB). Measurements were done to cover the 250-10000 Hertz (Hz) frequencies. All audiometric data were evaluated according to standards of the American Academy of Otolaryngology Head Neck Surgery Hearing and Balance Committee.

Statistical Analysis

Data analysis was done using the "IBM SPSS (Statistical Package for Social Sciences) for Windows 21 software package (SPSS Inc;Chicago,IL,USA). Definitive statistics were presented as mean \pm standard deviation for normal distributed variables, median (min-max) for non-normal distributed variables and nominal variables were shown as case number and percentage (%).

When the number of groups was two, the significance of the difference between the groups was analyzed with t-test, significance of median values was analyzed with the Mann-Whitney U test. $P < 0.05$ was considered as statistically significant.

Results

Two groups were formed in this study. Group 1 consisted of 20 patients with a diagnosis of Sjogren's syndrome and who received hydroxychloroquine. Group 2 consisted of 15 patients with the diagnosis of Sjogren's syndrome who did not start to receive hydroxychloroquine.

The average age in group 1 was 51.8, whereas 42.6 in group 2. There were 18 female and 2 male patients in group 1. There were 10 female and 5 male patients in group 2. There is not any significant difference between the groups in terms of Male/female ratio ($p > 0.05$). Demographic characteristics are shown in Table 1.

In group 1 all patients had complaint about mouth and eye dryness but after using hydroxychloroquine these symptoms decreased. One patient had severe joint involvement. In group 2 eleven patients had dryness in mouth and five patients have dryness in eyes. None of the patients had joint involvement.

Drug dosage was generally 2x200 miligrams (mg) in group 1 patients. Therefore, in order to standardize patient's drug intake,

Table 1: Demographic characteristics of the patients

	Group 1	Group 2
Persons	20	15
Females	18	10
Males	2	5
Average age	57.1	42.9

dosage calculation was done by multiplying daily 200 mg tablet with total year of drug use. Tablet/year was interpreted as the unit. According to this calculation, the average drug dosage was 7.8 tablets/year. That means the group 1 patients used drug 2*200 daily for 7.8 years averagely.

Tinnitus was present in 55% of the patients in group 1. Tinnitus was present in 6.7% of the patients in group 2. There was a statistically significant difference between the groups ($p>0.01$). In group 1, 15% of the patients complained of vertigo, while there was not any patients with vertigo in group 2.

There was not any statistically significant difference between the groups for either ear at 250 Hz, 500 Hz, 1000 Hz and 2000 Hz in audiogram ($p>0.05$). There was statistically significant difference at 4000 Hz in the left ear and 8000 Hz in the right ear and at 10,000 Hz in both ears in the audiogram ($p<0.05$). There was not any statistical significance at 4000 Hz in the right ear and at 8000 Hz in the left ear ($p>0.05$). Comparison of pure tone audiometric results based on Hz in group 1 are shown in Table 2. Comparison of pure tone audiometric results based on Hz in group 2 are shown in Table 3.

Discussion

Sjogren's syndrome is a chronic inflammatory disorder that leads to eye and mouth dryness and belongs to the autoimmune inner ear diseases group. It is believed that its first otologic sign is hearing loss. Sensorineural hearing loss, tinnitus and vertigo can be seen in autoimmune inner ear disease. Although its pathogenesis has not been clarified yet, inner ear immune complex vasculitis or autoantibody formation associated with antigenic epitopes are suggested as hypothesis (14,15).

In a study, 22.5% of 40 female patients with the Sjogren's syndrome suffered from sensorineural hearing loss. In another study, 30 patients with the Sjogren's syndrome were compared to 40 healthy individuals in terms of hearing loss. Sensorineural hearing loss was found in 48% of the patients with the Sjogren's syndrome (15,16).

Several studies reported that hearing loss in patients with the Sjogren's syndrome is related to the duration of the disease and it was pointed out that development of hearing loss is more likely when the duration of the disease is longer (16). Based on this information, it can be stated that in our study, too, hearing capability of the newly diagnosed patients is better than those who had been diagnosed earlier. However, it is not possible that duration of disease alone has an impact on hearing loss. There are studies supporting this, too (17). It is natural for hearing loss to develop as time passes due to aging. Besides, ototoxic drugs used in treatment of this disease can have this impact or they can facilitate development of hearing loss.

Hydroxychloroquine, one of the most commonly used drugs in the Sjogren's syndrome is known to induce ototoxicity and retinopathy (18).

Hydroxychloroquine retinopathy is seen in 0.1 to 0.5% of cases. Hydroxychloroquine retinopathy is rather uncommon. It is known that the risk increases in direct proportion to duration of drug use and cumulative dosage.

Although periodic ophthalmologic examination is recommended for retinal toxicity, changes on hearing that is induced by chloroquine and its ototoxic characteristics were not noticed and emphasized for a long time (18).

Cochleovestibular ototoxicity can occur following acute and chronic use as well as with high dosages. Studies suggest that chloroquine had an impact on melanocytes and fixated them; and because of its melanocyte content, it also affected stria vascularis that secretes endolymph and provides endolymphatic electrical potential; damaged cochlear sensorineural hairy cells, diminished the number of neurons in spiral ganglion, lowered the number of basilar membrane supportive cells, and induced atrophy in stria vascularis (7-10). This finding establishes the need for the early and periodic audiologic examinations during the treatment of the Sjogren's syndrome.

Ototoxicity of this drug, also used in the treatment of other diseases such as systemic lupus erythematosus, rheumatoid

Table 2: Comparison of pure tone audiometric results based on Hz in group 1 are shown in Table 2

	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz	10,000 Hz
Group 1 right ear	18.75 dB	17.5 dB	16.5 dB	17 dB	19.25 dB	30.5 dB	34 dB
Group 1 left ear	18.5 dB	16.25 dB	15.5 dB	16.75 dB	22 dB	28 dB	32.75 dB

Table 3: Comparison of pure tone audiometric results based on Hz in group 2 are shown in Table 3

	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz	10,000 Hz
Group 2 right ear	16 dB	14 dB	12 dB	14 dB	14 dB	18 dB	20 dB
Group 2 left ear	16 dB	14 dB	12 dB	14 dB	14 dB	20 dB	19.33 dB

arthritis, idiopathic pulmonary hemosiderosis, occurs following long term use (10,19,20). Several studies reported that ototoxic effects of hydroxychloroquine arise following long term use. However, in one study, sudden bilateral sensorineural hearing loss was seen in an eleven-year-old female patient who was newly given hydroxychloroquine treatment for systemic lupus erythematosus; this suggested that hydroxychloroquine can cause ototoxicity independent from time of use (21).

Kabasakal et al. (22) reported that average time between onset findings and diagnosis of the Sjogren syndrome is 5.7 years. Therefore patients who have been diagnosed are exposed to autoimmune impacts without getting any treatment.

In our study, tinnitus complaints of the patients were also investigated. 55% of the patients in drug using group (group 1) and 6.7% (1 patient) of no-drug-using group (group 2) complained of tinnitus. Hydroxychloroquine can lead to tinnitus because it is a quinine-like drug (8). If tinnitus associated with the Sjogren's syndrome has a pathophysiology that develops over time, it is quite normal that tinnitus is more common in group 1. However, if the time between aforementioned onset findings and diagnosis can prolong as much as 5.7 years, it is strongly suggested that drug has an impact on tinnitus development since it occurs in only 6.7% of the newly diagnosed patients. When tinnitus was statistically compared between group 1 and group 2, significant results were found ($p<0.05$).

The main goal in audiological monitorization of ototoxicity is to detect the hearing loss before speech frequencies are lost. Thus, measures can be taken in order to prevent advance of hearing loss or slow it down. In certain cases where ototoxicity is unpreventable, monitorization is crucial for hearing rehabilitation. Today, three basic methods are used to detect ototoxic effects.

1. Standard audiometry
2. High frequency audiometry
3. Otoacoustic emission

In our study, pure tone audiometry was performed in the range of 250-10,000 Hz. When a comparison was done between group 1 and group 2 in the pure tone audiometry test, a statistically significant difference was found in the right ear at 8000 Hz and 10,000 Hz. Similarly, when the left ear results were evaluated, a statistically significant difference was noted at 4000 Hz and 10,000 Hz. Hearing thresholds that are accepted as normal up to 2000 Hz were obtained in both groups; whereas at frequencies of 4000 Hz and above hearing thresholds started to rise to above 20 dB in group 1.

Statistical Analysis

Analysis revealed that these results were significant. Although a statistical significance could not be obtained in

left ear at 8000 Hz between the groups, the average hearing threshold was determined as 28 dB. In group 2, however, average hearing threshold in left ear at 8000 Hz was 20 dB. Although statistically insignificant, this difference has a clinical meaning, because 0-20 dB is considered as a normal hearing threshold, and the concept of hearing loss comes into question at thresholds above 20 dB and above.

In literature, previous studies also reported that hearing loss is detected at frequencies 4000 Hz and above in the Sjogren's syndrome (15-17). In our study, on the other hand, patients newly diagnosed with the Sjogren's syndrome were compared with those who had been previously diagnosed. According to our findings, hearing loss could not be detected in patients with newly diagnosed Sjogren's syndrome. In patients who had previous diagnosis, sensorineural hearing loss was detected at high frequencies. Depending on this finding, it can be suggested that hearing loss associated with the disease can be related to duration of exposure to this disorder. There are studies that support this in the literature, however, another possible cause of hearing loss can be drug containing active substance of hydroxychloroquine that is often used in treatment of this disease. As duration of the disease increases, exposure to drug also increase.

The average age in group 1 is 57.1. It is 42.9 in group 2. Since age range was 40-60 years in both groups, the age factor was limitation of our study. There is not any statistically significant difference between two groups in terms of male/female ratio. Groups were similar in regard to other diseases and medical history of patients did not reveal any factor except for Sjogren's syndrome and use of hydroxychloroquine that could affect hearing. Hydroxychloroquine was generally prescribed as 200 mg tablets and twice daily. In order to bring a certain standardization, a tablet dosage/year formula was developed in our study. A patient who received the drug 2x200 mg for ten years was standardized as 20 tablets/year. A patient who received the drug 1x200 mg for ten years was standardized as 10 tablets/year. When a calculation was done for each patient, the average time for drug use was 7.8 tablets/year. In other group, none of the patients used this medication. Therefore, it was observed that as exposure to drug increased, hearing loss also increased. Patients who had the most severe hearing loss were those who were more exposed to drug use. According to this, it can be concluded that use of hydroxychloroquine has an enhancing impact on hearing loss in the Sjogren's disease.

Exposure time to drug is different between the two groups and if an unknown mechanism of ototoxicity in this disease gets worse depending on time, then hearing loss could have occurred due to this. It is known that duration of disease is reported to be longer because of late diagnosis in some studies in literature (22,23). Therefore, if hearing loss develops depending on time,

hearing loss can be seen in newly diagnosed patients. In our series, hearing threshold was detected in 2 patients at only 10,000 Hz 30 dB and 40 dB in the newly diagnosed patients group. Normal thresholds were obtained at other frequencies. However, considering the number of cases in our patient group, it is difficult to reach a definitive conclusion, thus further studies with larger patient groups are needed.

Conclusion

It is apparent that studies with larger groups are needed in order to understand whether hearing loss develops depending on time or not, and to detect hearing loss that can be associated with drug use. However, it is still challenging to understand the cause of hearing loss by this approach. Follow up of newly diagnosed patients who are planned to receive hydroxychloroquine treatment and those with a new diagnosis and no planned hydroxychloroquine treatment and analysis of the results can perhaps answer this question. Besides, anatomic and histologic examination of inner ears of these patients can clarify this issue. However, conducting such a study requires a long time and can bring up serious ethical problems, however, an animal model study that would be developed using this idea can contribute to literature.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Ankara University Medical School Ethical Committee (number: 2014-12-21).

Informed Consent: Taken from all of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., Y.I., Concept: M.G., Y.I., Design: M.G., Data Collection or Processing: Y.I., Analysis or Interpretation: M.G., Y.I., Literature Search: M.G., Y.I., Writing: Y.I., M.G.

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