

A Case of a Rare Side Effect of Hydroxychloroquine: Hallucination

Hidroksiklorokinin Nadir Bir Yan Etkisine Dair Bir Olgu: Halüsinasyon

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ABSTRACT Chloroquine and hydroxychloroquine are anti-malarial agents commonly used for the treatment of rheumatic diseases due to their anti-inflammatory effects. Herein, we present a case report of serious visual hallucinations in a patient who was under hydroxychloroquine treatment after the diagnosis of undifferentiated connective tissue disease. Hydroxychloroquine was given to a 23-year-old female patient without a history of psychiatric disease or drug use as a monotherapy. She developed severe visual hallucinations after the first week of treatment. After psychiatric consultation, the treatment was discontinued considering the potential occurrence of a side effect. After cessation of the treatment, her complaints were recovered completely in a week. Three months later the patient had similar complaints after chloroquine treatment initiation. Her complaints disappeared again after cessation of the second drug. In conclusion, the potential risk of development of drug-associated hallucinations in patients using chloroquine and hydroxychloroquine should be taken into consideration. It is very important to differentiate this adverse drug effect from the neuropsychiatric involvement of connective tissue diseases.

Key Words: Hydroxychloroquine; connective tissue diseases; hallucinations; adverse effects

ÖZET Klorokin ve hidroksiklorokin, antiinflatuvar etkilerinden dolayı romatizmal hastalıkların tedavisinde sıkça kullanılan antimalaryal ilaçlardır. Biz bu yazıda ayırım yapılamayan bağ doku hastalığı tanısı ile izlenen ve hidroksiklorokin başlanan bir hastada gözlenen ciddi görsel halüsinasyon vakasını sunduk. Bilinen psikiyatrik hastalığı ve ilaç kullanım öyküsü bulunmayan yirmi üç yaşında kadın hastaya tek ilaç olarak hidroksiklorokin başlandı. İlacın başlanmasından bir hafta sonra hasta görsel halüsinasyon şikayeti ile başvurdu. Psikiyatri bölümüne danışılan hastada ilaç yan etkisi düşünülerek ilaç kesildi. İlacın kesilmesinden bir hafta sonra hastanın şikayetleri tamamen düzeldi. Üç ay sonra klorokin tedavisi başlanmasıyla hastada benzer şikayetler gelişti. Hastanın şikayetleri ilacın kesilmesiyle yeniden tamamen düzeldi. Sonuç olarak; hidroksiklorokin ve klorokin kullanan hastalarda ilaca bağlı halüsinasyon gelişebileceği akılda tutulmalıdır. Bu ilaç yan etkisini, bağ doku hastalığına bağlı nöropsikiyatrik tutulumdan ayırt etmek çok önemlidir.

Anahtar Kelimeler: Hidroksiklorokin; bağ doku hastalıkları; halüsinasyonlar; istenmeyen etkiler

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Anti-malarial agents, chloroquine and hydroxychloroquine are commonly used for the treatment of rheumatic diseases due to their anti-inflammatory effects. Vision loss, cutaneous lesions, gastrointestinal disorders, alopecia and neuropathy are the common side effects of the antimalarial agents. These adverse effects are frequently associated with the chronic and high-dose administration of the drugs.

Chloroquine and hydroxychloroquine may very rarely lead to psychosis-like psychiatric side effects.¹

The term “*undifferentiated connective tissue diseases*” (UCTD) is used to describe the conditions characterized by the presence of signs and symptoms suggestive of a systemic autoimmune disease that does not meet the classification criteria for the defined connective tissue diseases. It exhibits no specific signs and symptoms. Approximately, 20 to 40% of the UCTD converts into differentiated connective tissue disease while 60% remain undifferentiated or completely improve.²

In this report, we present an undifferentiated connective tissue disease patient with serious visual hallucinations related to hydroxychloroquine treatment.

CASE REPORT

A 23-year-old female patient was admitted to the Rheumatology outpatient clinic with the complaints of pain that was particularly more severe in the wrists and metacarpophalangeal joints. On rheumatologic examination, she described Raynaud’s phenomenon, arthralgia for more than 3 months and morning stiffness lasting about 30 minutes. In her medical history, it was seen that she had been under follow-up due to leukopenia for the last 5 years. Her physical examination demonstrated no signs of arthritis. Raynaud’s phenomenon was observed in her hands. Nailfold digital capillaroscopy showed minor capillary changes not specific for scleroderma. No findings of a dry eye were detected on her ocular examination.

Her blood tests revealed a total white blood cell count of $2.86 \times 10^9/L$ (4.5-11), platelets; $152 \times 10^9/L$ (130-400) and a haemoglobin level of 11.7 g/dL (12-16), normal renal and hepatic function tests. Urinalysis was normal. Erythrocyte sedimentation rate and C-reactive protein (CRP) were within normal limits; 7 mm/h and 3 mg/L, respectively and RF was negative. The connective tissue laboratory investigations showed an antinuclear antibody (ANA) titer of 1:1280 with the nucleolar pattern while, anti-double-stranded DNA antibody,

anti-Smith antibody, anti-ribonucleoprotein, anti-SSA, anti-SSB and Coombs tests were negative, levels of complements C4 and C3 were 15.9 mg/dL (15–50 mg/dL), and 75.6 mg/dL (85–200 mg/dL) respectively. Anticardiolipin antibodies were also within normal limits. Her echocardiogram and chest X-ray showed no abnormalities. Based on these results, her diagnosis was undifferentiated connective tissue disease. Monotherapy with hydroxychloroquine was initiated a dose of 400 mg a day. The patient had in no history of established psychiatric disease or any drug use. She presented with the complaint of visual hallucinations one week after the initiation of the drug. We learned from her relatives that she felt being followed by someone, and she was even unable to go from one room to another in the house because she saw people radiating light. She was consulted by the department of psychiatry. According to Naranjo adverse drug reactions probability scale the patient’s total score was nine, indicating a definite adverse effect.³ The hydroxychloroquine treatment was stopped, considering the potential risk of such a side effect and no psychiatric drug was suggested. After the cessation of the treatment, her complaints diminished with time. One week later, her complaints completely disappeared. The patient, who was followed-up once a week for the first month and once every two weeks for the subsequent two months, didn’t exhibit any recurrence of her hallucinations. Three months later 250 mg chloroquine was given again to the patient. In the first week follow-up visit, her visual hallucination complaints restarted, and she was afraid of quietness. Her complaints completely vanished after she stopped using the drug.

DISCUSSION

A connective tissue disease with variable signs and symptoms, which does not meet the criteria for a specific disease, is called an “*undifferentiated connective tissue disease*”.² The main clinical manifestations at the onset of these undefined diseases include arthralgias, arthritis, Raynaud’s phenomenon, leukopenia, xerostomia, xerophthalmia, thrombocytopenia, pleuritis/pericarditis, peripheral

neuropathy and photosensitive rash. The clinical profile of UCTD is generally mild and is characterized by the absence of major organ involvement, particularly of the kidney and central nervous system. The serological findings are highly variable. A positive serology for antinuclear antibody (ANA) is common, with a positive rate ranging from 60% to 100%, and a stable profile over time.⁴ Anti Ro/SSA, anti-RNP and anti-dsDNA antibody positivities have been reported. However, no specific clinical or immunological parameters exist for establishing the diagnosis.⁵⁻⁷ NSAIDs, antimalarial agents and corticosteroids are the first-line therapeutic options for this disease. Antimalarials may be used with or without NSAIDs to control arthralgias/arthritis, constitutional symptoms, and the mucocutaneous manifestations.^{2,6}

Chloroquine phosphate and hydroxychloroquine sulphate are quinine derivative agents, for which had been initially used the treatment of malaria. After the discovery of the anti-inflammatory efficacy of these drugs, they have been used for the treatment of rheumatic diseases. These agents may inhibit the chemotactic properties of pro-inflammatory leukocytes (e.g., polymorphonuclear cells, lymphocytes). They may also interfere with the intracellular processing of the autoantigenic peptides.⁸ Despite their general safety, both drugs may cause serious toxicity.⁹ Chloroquine and hydroxychloroquine may very rarely lead to psychosis-like psychiatric side effects. Although little is documented on such presentations, they have been mainly described in patients receiving treatment for malaria. To the best of our knowledge, apart from the cases of malaria, the hallucinatory side effect of hydroxychloroquine was reported only in a case of lichen planus, and no

such side effect was reported in the treatment of rheumatic diseases.¹

Hallucinations are “false sensory perceptions, unfounded on external realities, and outside the cognitive control of the affected individual.” Hallucinations caused by drugs are usually visual. Although hallucinations may present as an isolated adverse effect, they often occur as a part of the drug-induced psychosis picture. Delirium, hallucinations, manic attacks or depression secondary to anti-malarial agents are very rarely observed in patients without any previous history of psychiatric diseases. The mechanism underlying this condition is not known; it is believed to occur as an idiosyncratic reaction.^{10,11} It can occur within several hours upto 40 days after the initiation of medication. It usually disappears within a week after discontinuation of the drug. There is no correlation between the dose of the anti-malarial agent administered and the severity of the emerging psychiatric disorder.¹ It can sometimes be difficult to differentiate if a hallucination is caused by a drug or an underlying illness. In our case chloroquine derivatives were given two times, and although two different agents were used both therapies resulted with similar side effects. Furthermore her complaints recovered within few day after cessation of both therapies. This situation suggested us that the patients' complaints were not related to her illness but side effects of the medical therapy.

In the follow-up of these agents commonly used the treatment of rheumatic diseases, one for should take into consideration the potential risk of side effects, including psychosis and hallucinations. This gains further significance, particularly in the connective tissue diseases where psychosis may occur as a neurological involvement of the disease such as systemic lupus erythematosus.

REFERENCES

1. Ferraro V, Mantoux F, Denis K, Lay-Macagno MA, Ortonne JP, Lacour JP. [Hallucinations during treatment with hydrochloroquine]. *Ann Dermatol Venereol* 2004;131(5):471-3.
2. Mosca M, Tani C, Bombardieri S. A case of undifferentiated connective tissue disease: is it a distinct clinical entity? *Nat Clin Pract Rheumatol* 2008;4(6):328-32.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
4. Zhang Y, Zhang FK, Wu XN, Wang TL, Jia JD, Wang BE. Undifferentiated connective tissue diseases-related hepatic injury. *World J Gastroenterol* 2008;14(17):2780-2.
5. Mosca M, Tani C, Talarico R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): simplified systemic autoimmune diseases. *Autoimmun Rev* 2011;10(5):256-8.
6. Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev* 2006;6(1):1-4.
7. Vaz CC, Couto M, Medeiros D, Miranda L, Costa J, Nero P, et al. Undifferentiated connective tissue disease: a seven-center cross-sectional study of 184 patients. *Clin Rheumatol* 2009;28(8):915-21.
8. Cooper RG, Magwere T. Chloroquine: novel uses & manifestations. *Indian J Med Res* 2008;127(4):305-16.
9. Nord JE, Shah PK, Rinaldi RZ, Weisman MH. Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. *Semin Arthritis Rheum* 2004;33(5):336-51.
10. Mohan D, Mohandas E, Rajat R. Chloroquine psychosis: a chemical psychosis? *J Natl Med Assoc* 1981;73(11):1073-6.
11. Alisky JM, Chertkova EL, Iczkowski KA. Drug interactions and pharmacogenetic reactions are the basis for chloroquine and mefloquine-induced psychosis. *Med Hypotheses* 2006;67(5):1090-4.