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Case Report
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Clomipramine-Induced Tinnitus

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ABSTRACT

Tinnitus is a severe medical condition that affects the quality of life. It is defined as the perception of sound produced by the body without a corresponding external acoustic stimulus. Pathological abnormalities can occur throughout the auditory system due to ototoxic drug use. Clomipramine is a tricyclic antidepressant used in clinical practice to treat various mental diseases. Although it is an effective antidepressant, it does have specific side effects. According to the literature, although clomipramine has been linked to central nervous system side effects, there is no evidence that it causes tinnitus. We present a 44-year-old male patient whose tinnitus symptoms began after using clomipramine and ended after the medication was discontinued. Tinnitus symptoms have been recorded in the literature due to antimalarial medicines such as quinine and chloroquine, nonsteroidal anti-inflammatory drugs, and acetylsalicylic acid. To the best of our knowledge, ours is the first case of clomipramine-induced tinnitus.

Keywords: Antidepressant, tinnitus, clomipramine

INTRODUCTION

Tinnitus is a medical condition defined as the perception of internal sounds that generally occur in the head without external acoustic stimuli, which significantly reduces the quality of life and seriously affects the mental health of individuals.[1] Tinnitus, characterized by an unformed acoustic structure such as buzzing or ringing, can be produced by pathological changes throughout the auditory system.[2] In most cases, sudden hearing loss develops due to initial lesions such as noise trauma, presbycusis, or ototoxic drug administration. Tinnitus can be caused by abnormal neuronal activity in the central auditory pathways due to these lesions.[2] Antimalarial drugs such as quinine, chloroquine, nonsteroidal anti-inflammatory drugs, and acetylsalicylic acid can produce reversible and dose-related tinnitus, especially when used for an extended period of time.[3]

Sedation, blurred vision, urine retention, and sweating are common side effects of clomipramine, a tricyclic antidepressant often used to treat mental illness such as major depressive disorder and obsessive-compulsive disorder (OCD).[4] Gastrointestinal side effects are typical when initiating clomipramine medication and may lead to early discontinuation of therapy.[5] The most common symptoms are nausea and vomiting, although others include appetite and taste abnormalities, epigastric discomfort, and diarrhea. Tremor, myoclonus, ataxia, stiffness, dizziness, drowsiness, and headache are central nervous system side effects of clomipramine.[6] Although there are publications and manufacturer reports suggesting a link between clomipramine and tinnitus in the literature,[7] we are not aware

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of any case reports that demonstrate such a link. We present a case report of a 44-year-old male patient who experienced tinnitus symptoms after using clomipramine.

CASE PRESENTATION

A 44-year-old married, high school graduate male patient who works as an accountant applied to our psychiatry clinic with the complaint of constantly having thoughts of "blasphemy against God" and "my loved ones will get sick." He applied for complaints of sleeplessness and lack of appetite due to his frequent praying and began walking outside due to negative thoughts that filled his head. The patient had no previous psychiatric diagnosis and treatment. After a complete anamnesis and psychiatric evaluation, the patient was diagnosed with OCD according to the Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria. Clomipramine was begun at 25 mg/day and gradually escalated to 150 mg/day every week. The patient scored 48 on the Yale-Brown OCD Scale. The patient reported a complaint of tinnitus in the control examination after the patient started using clomipramine 150 mg/day, and the patient who did not have any risk factors constantly heard a metallic ringing sound in his ear. Otolaryngology and neurology consultation were requested. There was no organic etiology identified that may explain the current condition due to complete blood count, central nervous system magnetic resonance imaging, neurological, and otolaryngological examinations for the etiology of the patient, who did not have any existing disease or drug usage. Clomipramine dosage was lowered to 100 mg/ day. The patient's problems subsided, regressed, and finally stopped. The patient's tinnitus complaint did not reappear during follow-ups, and the patient is still being treated with medication for OCD in remission. Tinnitus caused by clomipramine was identified as a "possible side effect" by the Naranjo Adverse Drug Reaction Probability Scale[8] (Naranjo Adverse Drug Reaction Probability Scale Score: 6).

DISCUSSION

In the present article, a male patient who developed tinnitus after the use of clomipramine is reported. The tinnitus of the patient was regressed by reducing the dose of clomipramine. The article can be considered important because it draws attention to the fact that clomipramine, as a drug frequently used in clinical practice, can cause such a side effect that negatively affects the quality of life at high doses.

Tricyclic antidepressants were originally designed in the 1950s and marketed later for treating depression.[4] Due to their side effects and lethality in overdose quantities, they have been replaced mainly by selective serotonin reuptake inhibitors and serotonin–norepineph rine reuptake inhibitors in depression management.[4] Tricyclic antidepressants continue to treat OCD and several other mental disorders, apart from depression, with varying degrees of efficacy and safety.[9] There have been case reports of clomipramine's side effects, which are often used in therapeutic practice. Most of the adverse effects associated with clomipramine therapy can be predicted from the drug's pharmacological properties, particularly its anticholinergic effects were frequently (43%) reported: these included dry mouth, excessive sweating, constipation, blurred vision, urinary retention, and mydriasis.[10] Tinnitus symptoms developed in our case with the administration of clomipramine. To the best of our knowledge, this case may be the first report from this perspective.

Tinnitus can be caused by a wide range of etiologies and pathogens.[11] Current widespread belief is that tinnitus is most likely caused by damage to the auditory system's peripheral, even when a disease cannot be diagnosed using routine clinical audiometry measurements.[12] According to animal research, an increased rate of spontaneous discharge in subcortical auditory neurons enhanced neuronal synchrony, and hyperactivity in the auditory cortex is related to tinnitus.[13,14] Subcortical hyperactivity is thought to be caused by a decrease in stimulus-focused activity, which causes centrally compensatory synaptic changes.[15]

It has been reported that tinnitus and psychiatric disease can be seen together at a high rate.[16] It is unclear whether tinnitus causes psychiatric disorders or whether tinnitus is a component of psychiatric disorders.[17] In our case, we cannot give a clear answer to this question. Although the temporal relationship and the regression of tinnitus with decreasing the drug dose indicate that tinnitus is associated with clomipramine, it should also be kept in mind that it may be a component of the disease.

The literature suggests that the limbic system and serotonin (5-HT) may play a role in tinnitus by their effect on the brain and auditory pathways.[18] Clomipramine, a tricyclic antidepressant, may cause tinnitus due to its serotonin reuptake inhibition mechanism. Although no significant impacts on the regulatory region of the 5-HTTLPR (5-HT transporter) SLC6A4 gene have been identified in human genetic studies, serotonergic 5-HTTLPR modulation has been reported to cause tinnitus.[19] Serotonin has been shown in studies to have a modulating role in the genesis of tinnitus, although indirectly.[20] In this context, clomipramine may produce tinnitus in our case due to neuronal hyperactivity. However, with an unknown mechanism, clomipramine may have caused tinnitus by causing biochemical and electrophysiological changes in the inner ear or impaired impulse conduction in the eighth cranial nerve.[21] Such a possible mechanism indicates ototoxicity. It is important for clinicians to keep this possibility in mind in order to prevent permanent hearing pathologies. In addition, it should be kept in mind that clomipramine may cause tinnitus by a mechanism different from the possibilities mentioned here.

Drug side effects can be evaluated with the Naranjo Adverse Drug Reaction Probability Scale, which consists of 10 items developed by Naranjo et al.[8] According to the scale, where 0-13 points can be obtained according to the rating, 9 points and above are evaluated as "definite," between 5 and 8 points as "probable," between 1 and 4 points as "possible," and 0 points as "doubtful." The case was scaled according to this scale; Because there was a previous report of tinnitus due to clomipramine use (1 point), because the tinnitus developed after the administration of the suspected drug (2 points), no other cause other than the drug could cause tinnitus. (2 points) gets a total of 6 points due to the increase or decrease in the effect depending on the dose (1 point). This information suggests that the side effect is most likely caused by clomipramine.

As a result, tinnitus is a condition that significantly reduces an individual's quality of life. Because risk factors for clomipramine-induced tinnitus are unknown, clinicians should consider possible side effects with serotonin reuptake inhibition mechanisms, especially clomipramine. More thorough and controlled investigations are required to fully understand the tinnitus symptoms associated with clomipramine usage.

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REFERENCES

1. Henry JL, Wilson PH. *Tinnitus: A Self-Management Guide for the Ringing in Your Ears*. Allyn and Bacon; 2002.
2. Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. *Lancet Neurol*. 2013;12(9):920-930. [CrossRef]
3. Ralli M, Lobarinas E, Fetoni AR, Stolzberg D, Paludetti G, Salvi R. Comparison of salicylate and quinine induced tinnitus in rats; development, time course and evaluation of audiological correlates. *Otol Neurotol*. 2010;31(5):823-831. [CrossRef]
4. Stern RS, Marks IM, Mawson D, Luscombe DK. Clomipramine and exposure for compulsive rituals: II. Plasma levels, side effects and outcome. *Br J Psychiatry*. 1980;136(2):161-166. [CrossRef]
5. Ananth J, Assalian P, Links PS. Intolerable side effects of clomipramine. *J Clin Psychopharmacol*. 1982;2(3):215-216. [CrossRef]
6. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP*. 1990;24(7-8):739-744. [CrossRef]
7. Ackerman DL, Greenland S, Bystritsky A, Katz RJ. Relationship between early side effects and therapeutic effects of clomipramine therapy in obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1996;16(4):324-328. [CrossRef]
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. [CrossRef]
9. Baldo P, Doree C, Molin P, McFerran D, Cecco S. Antidepressants for patients with tinnitus. *Cochrane Database Syst Rev*. 2012;2012(9):CD003853. [CrossRef]
10. Langguth B, Landgrebe M, Wittmann M, Kleinjung T, Hajak G. Persistent tinnitus induced by tricyclic antidepressants. *J Psychopharmacol*. 2010;24(8):1273-1275. [CrossRef]
11. Mendis D, Johnston M. An unusual case of prolonged tinnitus following low-dose amitriptyline. *J Psychopharmacol*. 2008;22(5):574-575. [CrossRef]
12. Feder R. Tinnitus associated with amitriptyline. *J Clin Psychiatry*. 1990;51(2):85-86.
13. Racy J, Ward-Racy EA. Tinnitus in imipramine therapy. *Am J Psychiatry*. 1980;137(7):854-855. [CrossRef]
14. Evans DL, Golden RN. Protriptyline and tinnitus. *J Clin Psychopharmacol*. 1981;1(6):404-406. [CrossRef]
15. Sadock BJ, Sadock VA. *Ruiz P. Kaplan and Sadock's Synopsis of Psychiatry*. New York, NY: Lippincott Williams & Wilkins; 2014.
16. McKenna L, Hallam RS, Hinchcliffe R. The prevalence of psychological disturbance in neurotology outpatients. *Clin Otolaryngol Allied Sci*. 1991;16(5):452-456. [CrossRef]
17. McFerran DJ, Baguley DM. The efficacy of treatments for depression used in the management of tinnitus. *Audiol Med*. 2008;6(1):40-47. [CrossRef]
18. Simpson JJ, Davies WE. A review of evidence in support of a role for 5-HT in the perception of tinnitus. *Hear Res*. 2000;145(1-2):1-7. [CrossRef]
19. McTavish D, Benfield P. Clomipramine. An overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs*. 1990;39(1):136-153. [CrossRef]
20. Eggermont JJ. Pathophysiology of tinnitus. *Prog Brain Res*. 2007;166:19 -35. [CrossRef]
21. Seligmann H, Podoshin L, Ben-David J, Fradis M, Goldsher M. Drug-induced tinnitus and other hearing disorders. *Drug Saf*. 1996;14(3):198-212. [CrossRef]