INTRODUCTION

Fluvoxamine, which is a member of the selective serotonin reuptake inhibitors (SSRI), is a widely prescribed antidepressant. It is true that SSRIs all have several properties in common, not the least of which is the blockade of the serotonin transporter that leads to elevation of serotonin levels throughout the central nervous system (CNS) and also throughout the entire body. Increases in serotonin levels in specific regions of the brain result in the therapeutic actions of the SSRIs.

Unfortunately, the action of SSRIs on the serotonin transporter is not regionally specific, and elevation in serotonin levels in some regions of the CNS and peripheral nervous system lead to side effects (1). The most common adverse reactions to the SSRIs are gastrointestinal and neuropsychiatric, such as nausea, headache, and tremor (1,2).

It is also known that in the central auditory pathway, serotonin can be found in many structures, from cochlear nuclei to the auditory cortex, constituting one of the most important neuromodulatory circuits in hearing processing.
Serotonin (5-HT) transmission forms a major modulatory network within sensory systems. This network influences various information-processing mechanisms and, in particular, filtering of auditory information (4).

Prior research has shown serotonergic pathways to interface with the auditory system, although the exact role of serotonin in the auditory system is not well characterized (5). Serotonin decreases cochlear blood flow, which could lead to cochlear microcirculation dysfunction (6). Recently there are animal and human studies investigating the effect of serotonin on the auditory neurophysiology (4,5-7) with promising results. Tadros et al (6) suggested that the upregulation of 5-HT-2B receptor gene expression with age may contribute to age related hearing loss pathogenesis.

Regarding the effects of serotonin on the hearing process, SSRIs could also be expected to cause side effects related to hearing. There are studies concerning the therapeutic effects of SSRIs in tinnitus and hearing process (8). On the contrary, it is also known that SSRIs, namely fluoxetine (9) and paroxetine (10) can cause tinnitus as a possible side effect.

A role of serotonin in persistent tinnitus was postulated by Simpson and Davies (11), based on the consideration that disrupted or modified 5-HT function might cause a reduction in auditory filtering abilities and in tinnitus habituation (12).

Up to now, there has been only one case report about subjective hearing impairment accompanied with eye tics during treatment with fluoxetine (13). To our knowledge, association of fluvoxamine with tinnitus and hearing loss has not been reported before.

The aim of this paper is to report a case in which tinnitus and objective hearing loss was observed during fluvoxamine treatment and underline the possible effects of SSRIs on the hearing process.

**CASE REPORT**

A 54-year-old female patient was diagnosed with major depression by the psychiatrist and she was placed on fluvoxamine (50mg/day) for two weeks. Later fluvoxamine was increased to 100 mg /day and the patient noticed a tinnitus and diminished hearing in her right ear ten weeks after the initiation of the therapy. Regarding these complaints, she was referred to the otolaryngology department. There were no significant abnormality in medical history and no history of hearing problems in the past. The patient was not on any other medication other than fluvoxamine. Ear-nose-throat examination was completely normal.
Upon further investigation, pure tone audiometry revealed a mixed hearing loss with about 35 dB threshold at 250, 500, 1000 Hz in the right ear, whereas the hearing levels at other frequencies were normal. Ipsilateral and contralateral acoustic stapedial reflex thresholds were found to be elevated (100 dB) in the pathological ear. Transient otoacoustic emission recordings (TOAE) revealed low reproducibility (40%) and low signal to noise ratio (SNR) (1.37 dB) in the right ear (Figure 1). Fluvoxamine was discontinued and the patient reported that tinnitus and hearing loss disappeared after approximately six weeks. Upon control audiometry in the 7th week following discontinuation of fluvoxamine, hearing threshold levels improved to 20 dB on the control pure tone audiometry. Ipsilateral and contralateral acoustic stapedial reflex thresholds were found to be within normal limits, that is 80 dB. Reproducibility and SNR increased to be 75% and 7.76 dB respectively (Figure 2), indicating an improvement of TOAE scores of the patient after discontinuation of fluvoxamine. Moclobemide 300 mg/day was started for the depressive symptoms and later it was increased to 450 mg/day. Follow-up interview after 4 weeks and 8 weeks revealed that the depressive symptoms started to resolve and there wasn’t any hearing problem.

DISCUSSION

The unique side effects of different SSRIs have more to teach us about the mechanisms of the particular agent and the effects of serotonin on different parts of the brain (1). Although it is known that serotonin and thus SSRIs have a potential to interfere with auditory functions, to our knowledge, regarding SSRIs there has been only one case report suggesting an association between fluoxetine and hearing loss so far. In that patient, subjective hearing loss and eye tics appeared three weeks after starting fluoxetine 20 mg/day. Both eye tics and hearing loss improved to fully after approximately two weeks following the discontinuation fluoxetine but reappeared on readministration. These findings were interpreted by the authors as a possible mechanism of fluoxetine to interfere with facial nerve functioning (13).

At this point, it is interesting that Xia (7) reported fluoxetine to cause a biphasic effect on auditory cortex, increasing the spike and burst rate and burst duration at low concentrations of 1-10 µM, but beginning to decrease the network activity at 15 µM. Although it is known that the therapeutic plasma concentration of fluoxetine is 1 µM, since fluoxetine is lipid soluble with a high brain to blood ratio (7), the brain concentration can reach 20 µM.
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(7,14), and thus can cause an inhibitory effect on the auditory cortex. In our patient, the hearing deficit appeared in the tenth week of treatment and thus rather later in the treatment course than the case above. However, the possibility of a subthreshold hearing deficit, which might not have been recognized by the patient until the tenth week, should also be taken into consideration. On the other hand, the hearing symptoms disappeared six weeks after the discontinuation of fluvoxamine in our patient and this time period is longer than that of Cunningham et al.'s patient, in which the time for the disappearance of the symptoms was reported to be two weeks. However it should be kept in mind that both the appearance and the resolution of the hearing deficit were subjective in Cunningham et al.'s case. In our case we did not prefer to readminister fluvoxamine due to possible potential of SSRIs to interfere with auditory functions.

Preclinical studies suggest that fluvoxamine has effects at $\sigma_1$-receptors (15). $\sigma$ receptor modulates the N-methyl-D-aspartate (NMDA)/glutamate receptor (16,17). The $\sigma_1$-receptor is abundant in the dentate gyrus of the hippocampal formation, facial nucleus, and various thalamic and hypothalamic nuclei (18).

Our patient had a mixed hearing loss in the right ear which developed during fluvoxamine treatment and resolved after discontinuation of fluvoxamine. This finding was verified by objective measurements consisting of audiometry and TOAE recordings. Since the ear-nose-throat examination was completely normal, with no history of hearing problems in the past, and the patient was not on any other medication, the symptoms are most likely to be associated with fluvoxamine use.

This effect of fluvoxamine could be caused either by interfering with the facial nerve function as suggested by Cunningham et al. (13), by affecting the facial nucleus by way of its effect on $\sigma_1$ receptors, and/or by affecting the sensorineural auditory functions related to its serotonin altering capacity.

One other possibility is that the hearing impairment was coincidental with fluvoxamine treatment in our patient. However, in our opinion, regarding the growing body of literature concerning the relationship of serotonin with auditory mechanisms, this case is noteworthy to report and should not be overlooked. Further controlled studies are warranted to clarify the effects of SSRIs in general and fluvoxamine in particular on the hearing process.

References:

