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Tics Induced by Mirtazapine in an Adolescent

Abstract

Mirtazapine (MTZ) is an antidepressant approved by the FDA whose mechanism of action involves antagonism of alpha-2, H1, 5-HT2A, 5-HT2C and 5-HT3 receptors.Tics are sudden, rapid,purposeless, recurrent, non-rhythmic motor movements or vocalizations. There have been previous case reports of various medications causing tics. In this article, we report tic symptoms that we thought developed in association with mirtazapine treatment.

Keywords: Mirtazapine; Tics; Adolescent; Post-traumatic stress disorder

INTRODUCTION

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by blocking adrenergic alpha2-autoreceptors and alpha2-heteroreceptors, H1 as well as 5-HT2A, 5HT2C and 5-HT3 receptors (1,2). Mirtazapine is approved for the treatment of major depressive disorder (3,4). However, it is used off-label for the treatment of post-traumatic stress disorder, insomnia, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, and headaches(5–8). Tics are involuntary, sudden, rapid, repetitive, non-rhythmic motor movements or vocalizations(9). In this article, we present the tics that emerged after mirtazapine treatment in a 15-year-old male case who had no tics before and was followed up with post-traumatic stress disorder and depressive disorder and was started on mirtazapine due to predominant sleep problems.

CASE

A 15-year-old male patient from Çanakkale, currently attending high school, presented with symptoms of difficulty falling asleep, frequent awakenings, re-experiencing, and anxiety.The patient witnessed his mother's suicide attempt a week before his first admission.The patient had no known chronic disease and no medication use for any medical reason. It was learned that his mother has been followed up and treated for depressive disorder and panic disorder since 2014. In the family history the mother continues her treatment for depressive disorder, the father received psychopharmacological treatment in the past due to anger problems and has voluntarily stopped his treatment. Parental problems have been stressing the patient since early childhood. The patient's academic success is low and this situation leads to problems in the family. The patient spends time outside of school either working with his father or socializing with two close peers.The patient, who had no previous psychiatric history, was followed up with psychotherapeutic interventions for the first month. In his psychiatric evaluation, it was determined that he had symptoms of post-traumatic stress disorder and depressive symptoms. Mirtazapine 7.5 mg treatment was started because his symptoms continued 1 month after his first admission. The patient described involuntary eyebrow raising and involuntary movement of the legs that occurred on the 2nd day of treatment in the interview 2 weeks later. In the neurological examination performed on the patient, no abnormalities such as decreased muscle strength, paraesthesia or rigidity were observed. The neurological examination was unremarkable. All cranial nerves were intact, with motor strength 5/5 in all extremities and no signs of atrophy or fasciculations. Sensory testing was normal, deep tendon reflexes were symmetric and normal, and plantar responses were flexor.

Coordination tests were completed without difficulty, and gait, including walking on heels and toes, was normal. When the involuntary movements were evaluated in detail, they included features such as being suppressed but emerging more severely with increasing tension and not occurring during sleep. Involuntary movements were evaluated as tics. According to the information obtained from the patient, there was no one in his family diagnosed with tic disorder. He did not have any complaints or records related to tics in the past. There was no history of any neurological disorder, past infections, or the use of pharmacological agents other than mirtazapine that could account for the patient's current tics.Although the patient had been through stressful periods for many years, he did not show any tic symptoms before mirtazapine treatment. In this interview conducted with the patient two weeks after starting mirtazapine, the Yale Global Tic Severity Scale (YGTSS) was used to measure the severity of tic-like movements(10). The total score for motor tics was 11, and the impairment score was 30. The Yale Global Tic Rating Scale (YGTSS) is a common scale used to assess tic disorders. The scale is designed to measure the severity, frequency, and effects of both motor (movement) and vocal (voice) tics. This scale is frequently used in clinical follow-up, especially to assess the effectiveness of treatment and to monitor the course of the disease. The application of the scale in a Turkish sample and its validity and reliability study were conducted by Zaimoğlu et al(11)**.**

Due to the reduction in symptoms of difficulty falling asleep, frequent awakenings, and anxiety with mirtazapine treatment, tic severity was planned to be followed up. Mirtazapine treatment was continued at 7.5 mg/day for 2 months. No change was made in the mirtazapine dose due to the presence of tics. Six interviews were held during the follow-up period with mirtazapine. Throughout the follow-up process, there was no change in the severity and frequency of tics. Tics were followed with Yale Global Tic Severity Scale (YGTSS) during the interviews during this process. There was no change in YGTSS score during the treatment process with mirtazapine 7.5 mg/day. After 2 months of follow-up, mirtazapine was discontinued because the tics did not decrease and the patient complained about this condition. The patient reported that after discontinuing mirtazapine, his tics decreased starting the next day and disappeared within a week. In the interview conducted with the patient two weeks after discontinuation of mirtazapine, the Yale Global Tic Severity Scale (YGTSS) score was zero. The patient did not receive psychopharmacological treatment for 2 months after the discontinuation of mirtazapine treatment and was followed with psychotherapeutic interviews. The YGTSS score in the psychotherapeutic interviews was zero. After the mirtazapine was discontinued, the stressors continued and tics were not observed. In the following period, an increase in depressive symptoms and anxiety symptoms was observed. The patient was offered to restart mirtazapine treatment because the initial complaints, except for the tic symptoms, decreased with mirtazapine, but the patient did not accept. Sertraline treatment was started. Sertraline 50 mg/day treatment was continued for 2 months. No tics were observed during this period, YGTSS was zero. Depression and anxiety symptoms decreased. The patient terminated sertraline treatment at his own request. The patient did not want to use medication. He was followed up with psychotherapeutic interviews for 2 months. The Naranjo Algorithm is a standardized tool used to assess the likelihood that an adverse drug reaction is caused by a specific medication(12). The Naranjo score for mirtazapine-associated tics is 7. No tics were observed for 8 months after discontinuation of mirtazapine.

DISCUSSION

Mirtazapine-associated tics are a very rare condition, and to our knowledge, this is the second case reported in the literature. A review of movement disorders associated with mirtazapine in

the literature has been examined(13). In the review, 69 restless legs syndrome, 35 tremors, 10 akathisia, 9 periodic limb movement disorders, 6 dystonia, 4 rapid eye movement sleep behavior disorders, 3 dyskinesia, 2 parkinsonism and only 1 tic case were reported. It has been observed that mirtazapine-related tics have not been reported so far, except for the tic case mentioned in the review(14). In the reported case, a 17-year-old patient diagnosed with major depressive disorder developed tic attacks following mirtazapine administration.

Tics have a complex etiology(15,16). The exact neural mechanisms underlying tic generation remain to be fully elucidated(17). However, in general, tics are believed to arise from the failure of inhibitory mechanisms within a cortico-striato-thalamo-cortical circuit that suppresses premonitory urges for movement(17). Within these circuits, the transmission of signals is regulated by various neurotransmitters, including dopamine, glutamate, gamma-aminobutyric acid (GABA), and serotonin(18). Alterations in neurotransmitters, primarily dopamine, as well as serotonin, noradrenaline, and GABA, play a significant role in the pathophysiology of tics(19–22). The tonic-phasic dopamine release hypothesis has been proposed for the dopaminergic mechanism of tics. An overactive dopamine transporter system may lead to reduced tonic (baseline) dopamine levels, which could create a system characterized by high concentrations of dopamine receptors and increased phasic dopamine release(19). The complex interaction between the dopamine and serotonin systems may contribute to the development of tics(23). Mirtazapine, through its effects on 5-HT1A and 5-HT2A receptors, can lead to an increase in dopamine level(24,25). The serotonergic system also contributes to the pathophysiology of tic. In a study measuring dopamine and serotonin levels using PET scans in patients with Tourette syndrome , it was suggested that there is a reduced binding potential of the serotonin transporter (SERT) and a decrease in the number of 5-HT2A receptors(20). Clonidine has been known for many years to reduce tics(26). Clonidine, an α2-adrenergic receptor agonist, alleviates tics by activating presynaptic autoreceptors in the locus coeruleus, which reduces the release and turnover of norepinephrine(21,27). Stimulation of the noradrenergic system may contribute to the development of tics(28). The hyperadrenergic state caused by an increase in central Norepinephrine levels due to the antagonistic effect of mirtazapine at the alpha 2 receptor may also cause tics(28).

Some drugs may increase dopaminergic activity, causing tics to increase(29). The main treatment to suppress tics is Dopamine antagonists. Mirtazapine induces an increase in cortical dopamine output through its serotonergic and noradrenergic effects, along with α2-adrenergic receptor antagonism and facilitation of postsynaptic 5-HT1A receptor function(24). Although there is still no definitive information about the etiology of tics and the mechanism of mirtazapine-associated tics is not clear,it is suggested that it may be the result of the dopamine increase caused by the complex interaction between Serotonin, Noradrenaline and Dopamine systems(23,24).

In the case, the fact that the tic symptoms were observed immediately after mirtazapine medication, that they continued for 2 months during which mirtazapine treatment continued, and that they disappeared rapidly after mirtazapine treatment was discontinued, and that they were not observed during the 8-month period when mirtazapine was not used, strengthened the opinion that the tic symptoms that occurred were related to mirtazapine. The Naranjo score for the suspected drug reaction was 7, indicating a 'probable' relationship(12).

The similarities between the other case and our case are the age group of the patients (17 and 15 years old), gender, the absence of psychiatric diagnosis or pharmacologic treatment before their admission, the development of tic symptoms in a short time following mirtazapine

medication, and the decrease in tics shortly after mirtazapine was discontinued. The points of difference in the cases are that in the other case, the medication was continued for a short period of time, while in our case, mirtazapine medication was continued for 2 months. The dosage of medication we used was one-fourth of the other case.

The occurrence of tic symptoms due to mirtazapine is a rare phenomenon. It would be useful for clinicians to consider the possibility of developing tic symptoms during mirtazapine treatment. There is a need for studies investigating the relationship between tics and mirtazapine.

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Conflicts of Interest:

No potential conflict of interest relevant to this article was reported.

Author Contributions:

Conceptualization: Senem Yapar, Nurullah Bolat. Data acquisition: Senem Yapar. Formal analysis: Senem Yapar, Nurullah Bolat. Supervision: Nurullah Bolat. Writing−original draft: Senem Yapar, Nurullah Bolat. Writing−review & editing: Senem Yapar, Nurullah Bolat.

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