

Hyperkinetic Movement Disorders Induced by Mirtazapine: Unusual Case Report and Clinical Analysis of Reported Cases

Won Tae Yoon*

Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

Abstract

Background: Hyperkinetic movement disorders caused by mirtazapine are very rarely reported, and involuntary severe cervical and truncal dystonia as an initial manifestation of mirtazapine-induced hyperkinetic movement disorder have not yet been reported. This study aimed to report an unusual case and to investigate the clinical pattern of mirtazapine-induced hyperkinetic movement disorder.

Methods: We present a patient with involuntary severe cervical and truncal dystonia as an initial manifestation of mirtazapine-induced hyperkinetic movement disorders. Additionally, we review previously reported cases and analyse the clinical pattern of mirtazapine-induced hyperkinetic movement disorders.

Results: Among 12 cases including our case, the main features of hyperkinetic movement symptoms induced by mirtazapine are akathisia (n=5, 42%) and dystonia (n=4, 33%). The other movement symptoms were dyskinesia (n=2, 17%) and periodic limb movement disorder (PLMD)-like nocturnal movements (n=1, 8%). Major associated conditions were older patients with depression or previous medication history of multiple neuropsychiatric drugs.

Conclusion: The results of this clinically investigative study may provide support for the diagnosis of mirtazapine-induced hyperkinetic movement disorders. In addition, if there are hyperkinetic movement symptoms in older depressive patients taking psychiatric medications, including mirtazapine, a diagnosis of drug-induced hyperkinetic movement disorder caused by mirtazapine should be considered, and cessation of mirtazapine should be implemented as the best treatment of choice.

Keywords: Mirtazapine; Hyperkinetic movement disorder; Akathisia; Dystonia; Depression

Introduction

Mirtazapine is a commonly prescribed; efficacious antidepressant with a dual noradrenergic and specific serotonergic mechanism of action; it acts by blocking alpha 2 receptors in addition to selectively antagonizing the postsynaptic serotonin type 2 (5-HT₂) and type 3 (5-HT₃) receptors. Because mirtazapine differs from commonly used serotonin-norepinephrine and selective serotonin reuptake inhibitors; mirtazapine is deemed particularly safe and well tolerated [1,2].

Drug-induced hyperkinetic movement disorders can be caused by some drugs; including non-neuroleptic agents as well as psychotropic agents and dopamine-enhancing drugs [3]. One example of this type of drug is mirtazapine. However; mirtazapine-induced hyperkinetic movement disorders are extremely rare; and truncal and cervical dystonia induced by mirtazapine have not been reported.

The aim of this work is not only to report the clinically unusual phenotype of a mirtazapine-induced hyperkinetic movement disorder; which resulted in prominent extensor truncal and cervical dystonia; but also to review previously reported cases and to analyse the clinical pattern from the literature of patients who suffered from mirtazapine-induced hyperkinetic movement disorders.

Materials and Methods

Data acquisition and patients

By consultation from the psychiatric department; we identified one patient with severe cervical and truncal dystonia induced by mirtazapine. Written informed consent was obtained from the patient to publish all clinical data; videotaping; and brain imaging results for this article.

Furthermore, the PubMed database was screened for mirtazapine-induced movement disorders, mirtazapine associated with movement

disorders and side effects of mirtazapine from 1990 to June 2017 by searching the word "mirtazapine". From screening the PubMed database, 1921 articles were retrieved. Among these articles; only 11 cases with hyperkinetic movement disorders induced by mirtazapine were confirmed and 12 cases were included in the analysis including the case presented in this study and data from the reviewed literature. The inclusion criteria were as follows: reported cases presenting involuntary movement disorders and symptoms associated with mirtazapine or induced by mirtazapine. We excluded the case reports presenting medical problems and sensory complications without involuntary movement symptoms as a side effect of mirtazapine.

Statistical analysis

Collected data were analyzed by means of descriptive statistics (absolute and relative frequencies). Continuous variables were expressed as the mean \pm standard deviation (SD); and categorical variables were expressed as percentages.

Results

Case presentation

A 54-year-old Korean man was referred to our neurologic

*Corresponding author: Won Tae Yoon, Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, Tel: +82-2-2001-1840; Fax: +82-2-2001-2988; E-mail: wtyoon@gmail.com.

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department due to involuntary truncal and cervical movements. He presented relative sub-acute-onset; repetitive truncal and cervical dystonic movements two months ago. His truncal dystonic symptoms had become more aggravated in the lying position than in the standing or sitting position; so his upper trunk and neck muscles were continually waving; with prominent extensor muscles of the trunk in the lying position (Video Segment 1).

He had intermittent shortness of breath and chest tightness without other medical problems. He was diagnosed with depression and a panic disorder in another hospital; and he had taken mirtazapine medication; which were changed instead of low-dose paroxetine before the hyperkinetic movement symptoms occurred. He had no other medications and no history of substance abuse.

Other neurological examination; routine laboratory tests; brain imaging and electrophysiological tests were normal. In our department; he was clinically diagnosed as having mirtazapine-induced hyperkinetic movement disorder. After mirtazapine was discontinued; his dystonic symptoms gradually improved and completely resolved three weeks later (Video Segment 2).

Clinical analysis of hyperkinetic movement disorders induced by mirtazapine

Including the case presented in this study and data from the reviewed literature; we identified 12 cases of clinical confirmed hyperkinetic movement disorders induced by mirtazapine and summarized the clinical profiles of the 12 cases (Table 1) [4-13].

There were 6 women and 6 men (mean age 58.4 ± 16.1 years; range 28 to 79 years). The most common type of movement symptom induced by mirtazapine was akathisia (n=5; 42%); and the second type of movement symptom was dystonia; including Pisa syndrome (n=4; 33%). The other movement symptoms were dyskinesia (n=2; 17%) and periodic limb movement disorder (PLMD)-like nocturnal movements (n=1; 8%). There were no reports of other types of hyperkinetic movement disorders; such as chorea; myoclonus and tremor; and there were no reports of hypokinetic movement disorders; such as bradykinesia and parkinsonism.

In all 12 cases; the mirtazapine dosage at the time of onset of hyperkinetic symptoms has been documented. Six patients took 15 mg of mirtazapine; 5 patients took 30 mg of mirtazapine; and one patient had an additional 30 mg of mirtazapine on day 1 after taking 15 mg on day 3. Among 11 patients documented at the time of symptom onset after the duration of mirtazapine medication; 9 patients (75%) had onset of hyperkinetic movement symptoms within 9 days. Significantly; 5 patients (42%) had onset of hyperkinetic movement symptoms after a single dose in one day (30 mg single dose in 4 patients and 15 mg single dose in one patient).

The major associated conditions of the patients were depression and depressive illness (n=10; 83%). Other minor associated conditions were opioid dependence (n=1; 8%) and Alzheimer's disease (n=1; 8%). Two patients (17%) had not only depression but also other combined neuropsychiatric disorder (anxiety disorder and panic disorder). The time to improvement after cessation of mirtazapine medication was documented in 10 cases and varied from 4 hours to 3 weeks.

Among those patients with depression; all five patients (42%) with acute onset hyperkinetic movement induced by a single dose of mirtazapine improved within 3 days after cessation of taking mirtazapine medication; and two patients presenting severe akathisia symptoms improved after taking additional medication (Clonazepam and Diazepam). Seven patients (58%) had previous medication history of other psychiatric drugs before starting mirtazapine medication; which included mainly SSRIs (Paroxetine; Sertraline) or sedative medications (Fluvoxamine; Clonazepam; Flurazepam).

Discussion

To date; a few drug-induced movement disorder cases associated with mirtazapine have been reported; however; to the best of our knowledge; the case presented in this study is the first report of involuntary hyperkinetic movements of truncal and cervical dystonia as an initial manifestation of a mirtazapine-induced movement disorder in the literature. Additionally; this study is the first to analyze the clinical pattern in the literature of those who suffered from mirtazapine-induced hyperkinetic movement disorders.

Our case and analysis of other reported cases showed that the main

Author	Gender / Age	Type of hyperkinetic movement symptoms	Mirtazapine dosage / Duration of medication	Associated conditions	Time to improvement	Previous medication
Lu et al. [4]	M/63	Dystonia	15 mg / 9 days	Depression	4 days	No
Girishchandra et al. [5]	F/73	Akathisia	15 mg (3 days) and 30 mg (1 day)	Chronic depression	*NA	Fluvoxamine
Girishchandra et al. [5]	M/52	Akathisia	30 mg / Single dose (1 day)	Depressive illness	A few days by clonazepam 1mg	Various TCA and SSRIs
Konitsiotis et al. [6]	M/63	Dyskinesia (reversible)	30 mg / Single dose (1 day)	Major depression	4 hours	NA
Van den Bosch et al. [7]	F/79	Dystonia	30 mg / Single dose (1 day)	Alzheimer's disease	60 hours	NA
Gulsun and Doruk [8]	M/38	Akathisia	30 mg / Single dose (1 day)	Depressive disorder	30 minutes by diazepam 5mg †IV	NA
Markoula et al. [9]	F/72	Akathisia	30 mg / 20 years	Depression	2 days	No
Balez and Rektor [10]	F/76	Dyskinesia (gradual onset)	15 mg / 1 month	Depression and anxiety disorder	2 weeks	Clonazepam
Mattoo et al. [11]	M/28	±PLMD-like nocturnal movements	15 mg / 4 days	Opioid dependence	NA	Flurazepam
Guerrero et al. [12]	F/61	Pisa syndrome (truncal dystonia)	15 mg / Single dose (1 day)	Major depression	3 days	Sertraline
Raveendranathan and Swaminath [13]	F/42	Akathisia	15 mg / NA	Depressive episode	2 days	Paroxetine
Yoon [Present paper]	M/54	Truncal and cervical dystonia	15 mg / 7 days	Depression and panic disorder	3 weeks	Paroxetine

Note: *NA = Not available; †IV = Intravenous; ±PLMD = Periodic limb movement disorder

Table 1: Summary of hyperkinetic movement disorders induced by mirtazapine in reported cases and present case.

features of hyperkinetic movement symptoms induced by mirtazapine are akathisia and dystonia. Until now; other types of hyperkinetic movement symptoms; including myoclonus; chorea and tremor induced by mirtazapine; had not yet been reported in the literature. Additionally; there were no reports of mirtazapine-induced hypokinetic movement disorders such as bradykinesia and parkinsonism.

Mirtazapine is a commonly prescribed antidepressant with significant sedating and appetite-stimulating effects; it is a useful therapy for patients with sleeping difficulty and poor appetite as well as depression [14,15]. In some reports; mirtazapine might be helpful for reducing tremor symptoms of Parkinson's disease and essential tremors and for the treatment of antipsychotic-related akathisia [16-19]. However; based on our study results; differential diagnosis of mirtazapine-induced hyperkinetic movement disorder should be considered in patients with depression or other neuro-psychiatric disorders and hyperkinetic movement symptoms when further using mirtazapine medication.

In this study; most of the cases were associated with depression or other neuro-psychiatric disorders; and 7 of 12 patients (58%) were over the age of sixty. In addition; some case reports showed that one-time administration of mirtazapine medication could induce hyperkinetic movement symptoms. For these reasons; caution should be taken when giving additional prescriptions of mirtazapine to older patients who are taking multiple neuropsychiatric drugs for depression or a neuropsychiatric disease.

On the other hand; if patients with depression or other neuropsychiatric disorders who are taking multiple neuropsychiatric drug medications; including mirtazapine; present with hyperkinetic movement symptoms; mirtazapine-induced hyperkinetic movement disorders should be considered during neurologic examinations and routine laboratory tests for differential diagnosis of various movement disorders. Then; the cessation of mirtazapine medication might be recommended for at least three weeks for observation of changes in hyperkinetic movement symptoms and for confirmation of clinical diagnosis of mirtazapine-induced hyperkinetic movement disorders.

The pathomechanism and neurobiological basis of hyperkinetic movement disorders induced by mirtazapine have not been clearly defined. One study suggested that mirtazapine can induce hyperkinetic movement disorders; mainly akathisia; by blockade of the alpha 2-adreno-receptor if higher mirtazapine dosages are administered (over 30 mg/day); whereas low-dosage mirtazapine may be beneficial in treatment of akathisia with its marked serotonin (5-HT) 2A receptor blockade mechanism [16].

However; our study showed that low-dosage or short-term administration of mirtazapine might induce various hyperkinetic movement disorders; including dystonia; dyskinesia and PLMD as well as akathisia in some older patients or depressive patients having a medication history of taking multiple psychiatric drugs (especially SSRI or sedative medications). In light of dystonia induced by mirtazapine; the indirect; antidopaminergic action as a result of the 5-HT₂ receptor inhibition associated with the central noradrenergic effect would produce a noradrenergic-dopaminergic imbalance in favor of the former and might be the explanation for the appearance of the dystonia [20].

In agreement with prior literature; akathisia; dystonia; dyskinesia and restlessness are major components in mirtazapine-induced movement disorders. Mirtazapine-induced akathisia appears earlier and shows more rapid improvements than dystonia and dyskinesia. Additionally; if mirtazapine-induced akathisia is severe; clonazepam or diazepam would be helpful to reduce the akathisia symptoms; however; statistical significance was not achieved for further special treatments in severe cases by additional medications.

Conclusion

To our knowledge; this is the first case report of prominent extensor truncal and cervical dystonia induced by mirtazapine. As in this case; if there is acute- or sub-acute-onset; not-fixed; continual waving truncal and cervical dystonia with psychiatric medications; including mirtazapine; a diagnosis of drug-induced hyperkinetic movement disorders caused by mirtazapine should be considered; and cessation of mirtazapine should be used as the best treatment of choice.

Conflict of Interest

The author has no financial or personal relations that could pose a conflict of interest.

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