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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Guo-Xin Ni, MD, PhD, Chief Doctor, Professor, School of Sport Medicine and Rehabilitation, Beijing Sport University, Beijing 100084, China. guoxinni@fjmu.edu.cn

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CASE REPORT

Multiple therapies relieve long-term tardive dyskinesia in a patient with chronic schizophrenia: A case report

Liang Lv, Ping Guo, Min Feng, Yu Fang, Shi-Kai Wang, Huan-Xin Chen

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Liang Lv, Ping Guo, Min Feng, Yu Fang, Shi-Kai Wang, Department of Psychiatry, Huzhou Third People's Hospital Affiliated to Huzhou University, Huzhou 313000, Zhejiang Province, China

Huan-Xin Chen, Key Laboratory, Huzhou Third People's Hospital Affiliated to Huzhou University, Huzhou 313000, Zhejiang Province, China

Corresponding author: Shi-Kai Wang, PhD, Chief Physician, Department of Psychiatry, Huzhou Third People's Hospital Affiliated to Huzhou University, No. 2088 Tiaoxi East Road, Huzhou 313000, Zhejiang Province, China. wang-shikai@163.com

Abstract

BACKGROUND

Tardive dyskinesia (TD) is a serious and disabling movement disorder; it impairs social function and quality of life and increases the mortality rate. TD is usually induced by the use of antipsychotic drugs; however, the underlying mechanism remains unclear. Pharmacotherapy of TD includes cholinergic drugs, benzodiazepines, ginkgo biloba extract (GBE), antioxidants, amantadine, propanolol, botulinum toxin, valbenazine, and deutetrabenazine, whereas the non-pharmacotherapy approach includes modified electroconvulsive therapy (MECT) and deep brain stimulation. We successfully treated a chronic schizophrenia patient with comorbid long-term severe TD using deutetrabenazine, clozapine, and MECT.

CASE SUMMARY

A 69-year-old woman who was diagnosed as having schizophrenia 16 years ago developed severe TD after 6-mo prescription of risperidone oral solution. Her TD symptoms did not resolve despite various treatments, such as GBE, vitamin E, trihexyphenidyl, promethazine, benzodiazepines, and switching to quetiapine and olanzapine. After admission, she was given deutetrabenazine 6 mg bid. Her buccal tremor was slightly resolved 3 d later; however, her tongue remained protruded and could not be retracted. Quetiapine was switched to clozapine on day 4, and the buccal tremor remarkably resolved, and the tongue could be retracted into the mouth from day 6 onward. After three sessions of MECT, the buccal tremor resolved further. Since then, she has been able to take a semifluid diet, and her quality of life improved remarkably during 6 mo of follow-up.

CONCLUSION

TD is a serious condition which could be caused by antipsychotic medications; however, the best strategy against TD is prevention and monitoring during using antipsychotics. For patients with TD caused by antipsychotic medication use,

multiple measures should be considered like switching to clozapine, adjunction with deutetrabenazine, or even MECT.

Key Words: Tardive dyskinesia; Antipsychotics; Clozapine; Deutetrabenazine; Electroconvulsive therapy; Case report

Core Tip: Tardive dyskinesia (TD) is a serious and disabling movement disorder, and its pathogenesis remains unclear. This report describes the treatment of TD caused by risperidone in a schizophrenia patient, which could not be improved by switching to the other second-generation antipsychotics like quetiapine and olanzapine, neither by adjunction with medications like benzodiazepines, ginkgo biloba extract, or antioxidants. Her TD symptoms were relieved remarkably after multiple measures like switching to clozapine, adjunction with deutetrabenazine, and modified electroconvulsive therapy. Multiple measures are therefore recommended for TD treatment.

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INTRODUCTION

Tardive dyskinesia (TD) is a serious and disabling movement disorder, which usually occurs after long-term use of antipsychotic drugs. TD is defined as the involuntary tic or dance-like movement (lasting for at least several weeks) of the tongue, lower jaw, as well as the extremities[1]. It is evaluated with tools like the abnormal involuntary movement scale (AIMS)[2]. TD impairs social function and quality of life and increases the mortality rate[1,3].

Common risk factors for TD include first-generation antipsychotics (FGAs), age, sex, and long-term exposure to dopamine receptor blocking agents. In patients with schizophrenia, the prevalence of TD induced by antipsychotics is 20%-25%[4]. Although FGAs are much more likely to induce TD than second-generation antipsychotics (SGAs), the incidence of TD has been increasing with the widespread use of SGAs, including their off-label use[5].

Although the mechanism underlying TD pathogenesis remains unclear[6], there are three pathophysiological hypotheses for TD, namely, dopamine hypersensitivity, gamma-aminobutyric acid deficiency, and oxidative stress. The treatments for TD include pharmacotherapy and non-pharmacotherapy[7]. Pharmacotherapy includes the administration of cholinergic drugs, benzodiazepines, ginkgo biloba extract (GBE), antioxidants, calcium channel blockers, amantadine, propanolol, and botulinum toxin, whereas non-pharmacotherapy includes modified electroconvulsive therapy (MECT) and deep brain stimulation[8]. However, only valbenazine and deutetrabenazine (Austedo) have been approved by the United States Food and Drug Administration for treating TD. We successfully treated a chronic schizophrenia patient with comorbid long-term severe TD using deutetrabenazine, clozapine, and MECT. We herein report the details on this case.

CASE PRESENTATION

Chief complaints

Uncontrollable, abnormal, and repetitive movements of the tongue and lower jaw for 16 years.

History of present illness

A 69-year-old woman, who was diagnosed as having schizophrenia 16 years ago, was treated with risperidone oral solution for delusion and auditory hallucination. Six months later, her psychotic symptoms remitted, but she developed TD with abnormal involuntary movement in the mouth, tongue, and cheek. She was hospitalized twice since these symptoms appeared; however, her TD symptoms did not resolve despite various treatments, which included adjunction with GBE, vitamin E, trihexyphenidyl, promethazine, and benzodiazepines, as well as switching to quetiapine and olanzapine (Table 1). She has been on a liquid diet for many years because her teeth had to be removed due to severely worn tongue.

History of past illness

The patient was diagnosed as having schizophrenia 16 years ago. She was found to be hypertensive 2 years ago, which has been well controlled with valsartan 80 mg/d and amlodipine besylate 10 mg/d.

Table 1 Timelines of patient events and medications in current admission and follow-up

Date	Event	Medication/s	Comment
July 2008	Hospitalization	ROS 4 mg/d	First onset with delusion and auditory hallucination
November 2009	TD	ROS 4 mg/d + Alp 0.4 mg qn + GBE	Psychotic symptoms resolved, but her bucco-linguo-masticatory syndrome appeared and could not be relieved by GBE
November 09-18, 2010		Que 0.2 g/d + Alp 0.4 mg qn + GBE 1 tab bid + Vit E 0.1/d	TD was not relieved by switching ROS to Que and combining it with GBE and Vit E
November 19, 2011		Ola 10 mg/d + Alp 0.4 mg qn + GBE 1 tab bid + Vit E 0.1/d	TD was not relieved by switching Que to Ola and combining it with GBE and Vit E
October 12, 2020	Readmission	Ola 10 mg/d + PTZ 25 mg bid + THP 2 mg bid	TD was not relieved by a combination of PTZ and THP during hospitalization
October 21, 2020-June 08, 2022		Que 0.2 g/d + PTZ 25 mg bid + Vit E 0.1/d	TD was not relieved by switching to Que and combining it with PTZ and Vit E
June 09-11, 2022	Readmission	Que 0.1 bid + DTB 6 mg bid + Vit E 0.1/d + PTZ 50 mg tid + Alp 0.4 mg qn	TD was slightly ameliorated when administered in combination with DTB after admission; however, her tongue could not be retracted into the mouth. Video 1 (June 10, 2022). Baseline: AIMS 31, PANSS 56, CGI 7. D3: AIMS 29, PANSS 56, CGI 6
June 12-15, 2022		Clo 25 mg/d + DTB 6 mg bid + Vit E 0.1/d + PTZ 25 mg tid + Lor 1 mg qn	TD was relieved remarkably after switching Que to Clo, and her tongue could now be retracted into the mouth. Video 2 (June 14. 2022) D7: AIMS 23, PANSS 52, CGI 4
July 16-19, 2021		Clo 25 mg bid + DTB 6 mg bid + Vit E 0.1/d + PTZ 25 mg qn + Lor 1 mg qn + MECT for the first session	TD was ameliorated after combining MECT, and the tremor in her lower jaw was reduced. D10: AIMS 22, PANSS 48, CGI 3
July 20-22, 2021		Clo 25 mg bid + DTB 6 mg bid + Vit E 0.1/d + MECT for the second session	TD did not worsen after stopping Lor and PTZ
July 23, 2021	Discharge		D14: AIMS 20, PANSS 48, CGI 3
July 24, 2021-now		Clo 25 mg bid + DTB 6 mg bid	TD did not worsen after stopping Vit E, and she could take a semi-fluid diet. Video 3 (December 26, 2022). D182: AIMS 20, PANSS 46, CGI 3

AIMS: Abnormal involuntary movement scale; Alp: Alprazolam; Clo: Clozapine; DTB: Deutetrabenazine; GBE: Ginkgo biloba extract; Lor: Lorazepam; MECT: Modified electroconvulsive therapy; Ola: Olanzapine; PANSS: Positive and Negative Syndrome Scale; PTZ: Promethazine; Que: Quetiapine; ROS: Risperidone oral solution; TD: Tardive dyskinesia; THP: Trihexyphenidyl; Vit E: Vitamin E.

Personal and family history
The patient denied any personal or family history of other diseases.

Physical examination
The physical examination was not remarkable except for TD symptoms (Video 1). Mental examination showed clear consciousness, passive contact, poor thinking with delusion of reference, and depressive mood because of involuntary movements. Her insight was poor. She was not found to be experiencing hallucinations.

Laboratory examinations
After admission, many related examinations were conducted, but no abnormalities were found.

Imaging examinations
A head computed tomography scan revealed no abnormality.

FINAL DIAGNOSIS
The patient was diagnosed with schizophrenia, TD, and hypertension.

TREATMENT
After admission, the patient was given deutetrabenazine 6 mg bid. Her buccal tremor was slightly resolved 3 d later, but her tongue was still protruded and could not be retracted back. Quetiapine was switched to clozapine on day 4; consequently, the buccal tremor remarkably resolved, and the tongue could be retracted into the mouth from day 6

onward (Video 2). She was encouraged to undergo additional MECT. After obtaining written informed consent, she was given three sessions of MECT, and the buccal tremor resolved further. On day 14, she was discharged with the prescription of clozapine (25 mg bid) and deutetrabenazine (6 mg bid) (Table 1).

OUTCOME AND FOLLOW-UP

After discharge, the patient could take a semifluid diet with clozapine (25 mg bid) and deutetrabenazine (6 mg bid), and her quality of life improved remarkably during 6 mo of follow-up (Video 3, Table 1).

DISCUSSION

TD is mainly caused by FGAs and managed by lowering the FGA dose or switching to SGAs, or it can be treated with deutetrabenazine and valbenazine. In this case, TD was induced by taking 4 mg risperidone daily for 6 mo, and TD did not completely resolve after switching to other SGAs like quetiapine and olanzapine. This was a case of late-onset schizophrenia with possible hypersensitivity to risperidone. In this case, the underlying mechanism of TD could be that the plasma concentration of risperidone was high because of reduced metabolic function in older patients. It could also possibly be explained by reduced number of dopamine receptors, leading to increased sensitivity to SGAs[9,10]. This case suggests that SGA use is also associated with a high risk of developing TD in patients with late-onset schizophrenia, which should be monitored with instruments like AIMS.

The patient responded poorly to medications like GBE, vitamin E, benzodiazepines, and promethazine. Her TD symptoms resolved partially with deutetrabenazine, a selective vesicular monoamine transporter 2 inhibitor[11], but resolved remarkably with clozapine. Clozapine is associated with a low risk of TD, which may be due to its low affinity to and rapid dissociation with dopamine D_2 receptors[12], suggesting that TD can be aggravated by long-term binding of dopamine D_2 receptors.

TD symptoms and mental symptoms of the patient resolved markedly after three sessions of MECT. Although MECT is not a first-line recommendation for treating TD[13], it poses no risk of precipitating, aggravating, or perpetuating TD and may be an important alternative choice for TD treatment.

CONCLUSION

In summary, TD is a serious condition caused by long-term use of antipsychotic medications. The underlying mechanism of TD is complex and remains unknown. The best treatment strategy for TD is prevention and monitoring during using antipsychotics. When it comes to treatment, multiple measures like switching to clozapine or combining it with deutetrabenazine or MECT could lead to a better prognosis than a single treatment.

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FOOTNOTES

Co-first authors: Liang Lv and Ping Guo.

Author contributions: Lv L, Guo P, Wang SK, and Chen HX conceived, designed, and refined the study protocol; Lv L, Fang Y, and Feng M were involved in data collection; Lv L and Fang Y analyzed the data; Guo P drafted the manuscript; Wang SK and Chen HX revised the manuscript; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Lv L and Guo P contributed equally to this work as co-first authors. The reasons for designating Lv L and Guo P as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authors accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Lv L and Guo P contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Lv L and Guo P as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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