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Quetiapine Relieved Pisa Syndrome in Patient With Parkinson Disease

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Objectives: The aim of the study was to report quetiapine-relieved Pisa syndrome in a patient with Parkinson disease and to discuss the pathogenesis and treatment of Pisa syndrome.

Methods: We report a 74-year-old female patient with a history of Parkinson disease for 7 years. Pisa syndrome, lateral deviation of the spine and leaning to one side, appeared more than a year ago; adjusting levodopa was ineffective. After treatment with quetiapine for visual hallucinations, the patient's right side tilt was completely relieved after taking the drug for 1 month.

Conclusions: Drug-related Pisa syndrome may be associated with the imbalance in dopamine-choline. Pisa syndrome may have similar mechanisms and treatment options to dystonia.

This is the first report of quetiapine relieving Pisa syndrome in a patient with Parkinson disease.

Key Words: Pisa syndrome, quetiapine, Parkinson disease

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Pisa syndrome was first described by Ekbom et al[1] as a motor complication of antipsychotic drugs in 1972, an involuntary posture in which the trunk continued to be biased toward the side of the body. Later, Pisa syndrome was found to occur in a variety of neuropsychiatric patients. The first Pisa syndrome in patients with Parkinson's disease (PD) was reported in 2003.[2] There is no consensus on the diagnostic criteria of Pisa syndrome. The current widely used criterion is that the trunk bends at least 10° to one side, and this side bend is aggravated while standing, sitting, and walking and is reduced or disappears in the supine position.[3]

The presence of Pisa syndrome in some patients with PD is associated with the initiation or dose adjustment of dopaminergic drugs, including levodopa/carbidopa, levodopa/benserazide, levodopa/carbidopa/entacapone, ergotine (pegolide), and non-ergot derivatives such as pramipexole and ropinirole, and rasagiline.[4–11]

The cause of Pisa syndrome is unknown, and there are no specific treatments. Patients with PD with Pisa syndrome caused by anti-Parkinson drugs may stop taking the disease-causing drugs or adjust the drug dose, and some patients may be relieved of symptoms.[4–10,12]

CASE REPORT

The patient was an elderly woman, 74 years old, with a history of PD for 7 years. She had a history of mild glycemic abnormalities, had diet control, and was not taking medication for hypoglycemic therapy. In 2012, her left hand began to develop bradykinesia and resting tremor, and levodopa/benserazide 62.5 mg was given 3 times a day. Symptoms were relieved after taking the drug. After the patient's symptoms gradually worsened, the left lower limb and the right side of the limbs were slow and the body leaned forward.

FIGURE 1. Before taking quetiapine, when standing, right deviation of the lumbar spine.

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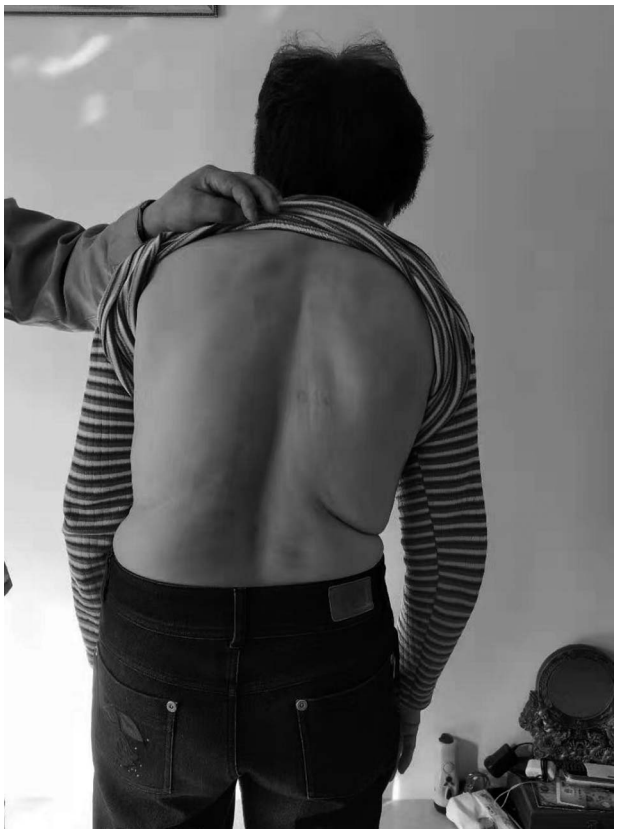

FIGURE 2. Before taking quetiapine, when standing, right deviation of the lumbar spine.

According to the condition, the medication was adjusted. In October 2016, the drug was adjusted to levodopa/benserazide 125 mg 3 times a day and pramipexole 0.5 mg 3 times a day. In January 2018, the patient developed a right deviation of the lumbar spine, standing and walking clearly, and the right tilt of the trunk was relieved in the supine position. The symptom had little effect on life, so the patient did not make drug adjustments until November 2018.

The patient's right side tilt symptoms gradually worsened. By November 2018, the limb stiffness was aggravated, and the right side of the spine was more inclined (Figs. 1, 2), but not present when supine (Fig. 3). The dose of levodopa/benserazide was adjusted to 187.5 mg 3 times a day, and the pramipexole dose was not adjusted. After adjusting the drug, the patient's limb stiffness was relieved, but the spine was tilted to the right without relief.

In July 2019, the patient developed visual hallucinations and was given quetiapine 75 mg twice daily. After taking the drug, the visual hallucinations gradually reduced, and the Pisa syndrome was significantly relieved; the symptoms were completely relieved after 1 month (Fig. 4). After 3 months, the patient still had no lateral bending of the trunk when walking and standing. After 1 year of taking the drug, there was no right deviation of the lumbar spine when walking (Fig. 5).

DISCUSSION

According to the 2015 Movement Disorder Society-issued diagnostic criteria for PD,[13] the patient has symptoms of bradykinesia, stiffness, and resting tremor, so Parkinson syndrome can be clearly diagnosed. There is no absolute exclusion of criteria and warnings. The effective treatment of levodopa and the resting tremor of a single limb are consistent with the support of PD diagnostic criteria, so the diagnosis of PD was diagnosed clinically.

At present, it is still controversial to use the spinal tilt angle of more than 10° or 15° as a diagnostic criterion for Pisa syndrome. Therefore, the incidence of Pisa syndrome in patients with PD is also inconsistent. Tinazzi et al[14] used a spinal tilt angle of more than 10° as a diagnostic criterion. A total of 1631 patients with PD were counted, and 143 of them had Pisa syndrome, with an incidence of approximately 8.8%. Pisa syndrome symptoms can be divided into acute, subchronic, and chronic, and most patients have chronic Pisa syndrome.[14] Acute Pisa syndrome in patients with PD is associated with the initiation of anti-PD drugs and dose adjustment.[15] The study found that the greater the daily dose of levodopa, the greater the likelihood of Pisa syndrome in patients with PD, and that levodopa combined with dopamine agonists may be more prone to Pisa syndrome.[14] The reported patient had Pisa syndrome after adjusting the dose of levodopa/benserazide and pramipexole for 1 year. The symptom was mild at the time of onset, and gradually worsened, showing chronic progression. Therefore, we believe that the appearance of Pisa syndrome in this patient may have little to do with drug adjustment, but may be related to the progression of PD.

To improve the limb stiffness, the dose of levodopa/benserazide was increased, and the motor symptom was alleviated, but the lateral deviation of the spine was not relieved, indicating that the Pisa syndrome had little relationship with the motor symptom. After the use of quetiapine for visual hallucinations, the

FIGURE 3. When supine, the right deviation of the lumbar spine was relieved.

FIGURE 4. After 1 month of taking the drug, the symptom of Pisa syndrome was completely relieved.

patient's Pisa syndrome was significantly relieved, and the symptom disappeared completely after taking the drug for 1 month.

There is currently no specific effective treatment for Pisa syndrome in patients with PD. Anti-PD–associated Pisa syndrome, after discontinuation or drug dose adjustment, some patients can be alleviated,[4–10,12] so it can be used as a first-line treatment option.[15] It has been reported[5] that patients with PD had Pisa syndrome in the off period, and the symptom was relieved after increasing the dose of levodopa. In addition, injection of botulinum toxin,[16] rehabilitation,[16] and Deep Brain Stimulation[17,18] may be effective.

Some non-PD patients have subacute Pisa syndrome associated with antipsychotics, including atypical antipsychotics.[19–22] In addition, antidepressants,[23,24] cholinesterase inhibitors,[25,26] and antiemetics[27] have been reported. The mechanism is still unclear. It may be that the abovementioned drugs directly or indirectly affect the dopamine-acetylcholine balance through neurotransmitters such as dopamine and serotonin (5-HT). Quetiapine is able to relieve Pisa syndrome in patients with PD and is also associated with dopamine-acetylcholine balance, and there may be other mechanisms.

The pathogenesis of Pisa syndrome is associated with a variety of factors, including sensory input (visual, proprioception, and vestibular), cortical sensorimotor integration, basal ganglia, and trunk muscle.[15] A variety of neurotransmitters are involved in the regulation of cortical and basal ganglia function. Drug-related Pisa syndrome may be associated with the imbalance in dopamine-choline

FIGURE 5. After 1 year of taking the drug, there was no right deviation of the lumbar spine when walking.

leading to dysfunction of the cortex and basal ganglia.[2] Dopamine replacement therapy further aggravates basal ganglia dysfunction caused by dopaminergic neuron loss and changes in dopamine receptor sensitivity.[28] Anti-PD drugs causing or alleviating Pisa syndrome may be due to the regulation of neurotransmitters. Quetiapine binds to dopamine D2 and 5-HT receptors, and we hypothesize that quetiapine also regulates dopamine-acetylcholine balance by regulating D2 and 5-HT to treat Pisa syndrome.

When patients with Pisa syndrome are supine, the tilt of the spine can be relieved obviously. This kind of action, not mechanical effect, can alleviate the abnormal posture. It is similar to the sensory trick of dystonia. Therefore, some scholars believe that there may be a relationship between Pisa syndrome and dystonia.[14,29,30] It has been reported that atypical antipsychotic drug clozapine is effective for dystonia.[31–34] Combined with our case reports, Pisa syndrome may have similar mechanisms and treatment options to dystonia to some extent.

We report for the first time that quetiapine relieved Pisa syndrome in a patient with PD, and we hope to provide new ideas for the pathogenesis and treatment of Pisa syndrome.

At present, the patient's lateral lean has basically disappeared, and the forward lean while walking has no significant change compared with a few months ago. After the patient was treated with quetiapine, her lateral tilt was significantly relieved, whereas the forward tilt was aggravated. I will continue to observe changes in the patient's condition.

REFERENCES

1. Ekbom K, Lindholm H, Ljungberg L. New dystonic syndrome associated with butyrophenone therapy. *Z Neurol* 1972;202:94–103.
2. Villarejo A, Camacho A, Garcia-Ramos R, et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol* 2003;26:119–121.
3. Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. *Lancet Neurol* 2011;10:538–549.
4. Cannas A, Solla P, Floris G, et al. Reversible Pisa syndrome in Parkinson's disease during treatment with pergolide: a case report. *Clin Neuropharmacol* 2005;28:252.
5. Kim JS, Park JW, Chung SW, et al. Pisa syndrome as a motor complication of Parkinson's disease. *Parkinsonism Relat Disord* 2007;13:126–128.
6. Cannas A, Solla P, Floris G, et al. Reversible Pisa syndrome in patients with Parkinson's disease on dopaminergic therapy. *J Neurol* 2009;256:390–395.
7. Fasano A, Di Matteo A, Vitale C, et al. Reversible Pisa syndrome in patients with Parkinson's disease on rasagiline therapy. *Mov Disord* 2011; 26:2578–2580.
8. Galati S, Moller JC, Stadler C. Ropinirole-induced Pisa syndrome in Parkinson disease. *Clin Neuropharmacol* 2014;37:58–59.
9. Solla P, Cannas A, Orofino G, et al. Rasagiline and Pisa syndrome in Parkinson's disease patients. *Neurol Sci* 2015;36:485–486.
10. Valentino F, Cosentino G, Fierro B, et al. Pisa syndrome after rasagiline therapy in a patient with Parkinson's disease. *Neurol Sci* 2015;36:2305.
11. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. *Mov Disord* 2005;20(Suppl 11):S11–S16.
12. Solla P, Cannas A, Congia S, et al. Levodopa/carbidopa/entacaponeinduced acute Pisa syndrome in a Parkinson's disease patient. *J Neurol Sci* 2008; 275:154–156.
13. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015;30(12):1591–1601.
14. Tinazzi M, Fasano A, Geroin C, et al. Pisa syndrome in Parkinson disease: an observational multicenter Italian study. *Neurology* 2015;85:1769–1779.
15. Barone P, Santangelo G, Amboni M, et al. Pisa syndrome in Parkinson's disease and parkinsonism: clinical features, pathophysiology, and treatment. *Lancet Neurol* 2016;15:1063–1074.
16. Tassorelli C, De Icco R, Alfonsi E, et al. Botulinum toxin type a potentiates the effect of neuromotor rehabilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. *Parkinsonism Relat Disord* 2014;20: 1140–1144.
17. Umemura A, Oka Y, Ohkita K, et al. Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease. *J Neurosurg* 2010;112:1283–1288.
18. Artusi CA, Zibetti M, Romagnolo A, et al. Subthalamic deep brain stimulation and trunk posture in Parkinson's disease. *Acta Neurol Scand* 2018;137:481–487.
19. Walder A, Greil W, Baumann P. Drug-induced Pisa syndrome under quetiapine. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33: 1286–1287.
20. Arora M, Praharaj SK, Sarkar S. Clozapine effective in olanzapine-induced Pisa syndrome. *Ann Pharmacother* 2006;40:2273–2275. https://doi.org/10.1345/aph.1H325.
21. Bruneau MA, Stip E. Metronome or alternating Pisa syndrome: a form of tardive dystonia under clozapine treatment. *Int Clin Psychopharmacol* 1998;13:229–232.
22. Chen HK, Wu BJ, Shao CH. Drug-induced Pisa syndrome associated with aripiprazole during clozapine treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:707–708.
23. Suzuki T, Kurita H, Hori T, et al. The Pisa syndrome (pleurothotonus) during antidepressant therapy. *Biol Psychiatry* 1997;41:234–236.
24. Perrone V, Antoniazzi S, Carnovale C, et al. A case of Pisa syndrome during sertraline and quetiapine treatment. *J Neuropsychiatry Clin Neurosci* 2012; 24:E31–E32.
25. Shinfuku M, Nakajima S, Uchida H, et al. Pisa syndrome caused by an acetylcholinesterase inhibitor in a patient with dementia with Lewy bodies. *Psychiatry Clin Neurosci* 2011;65:299.
26. Huvent-Grelle D, Boulanger E, Puisieux F. Relationship between Pisa syndrome and cholinesterase inhibitor use for elderly adults with Alzheimer's disease. *J Am Geriatr Soc* 2014;62:2450–2453.
27. Kropp S, Hauser U, Emrich HM, et al. Metoclopramide-related Pisa syndrome in clozapine treatment. *J Neuropsychiatry Clin Neurosci* 2001; 13:427–428.
28. Vitale C, Marcelli V, Furia T, et al. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Mov Disord* 2011;26:1458–1463.
29. Castrioto A, Piscicelli C, Perennou D, et al. The pathogenesis of Pisa syndrome in Parkinson's disease. *Mov Disord* 2014;29:1100–1107.
30. Michel SF, Arias Carrion O, Correa TE, et al. Pisa syndrome. *Clin Neuropharmacol* 2015;38:135–140.
31. Karp BI, Goldstein SR, Chen R, et al. An open trial of clozapine for dystonia. *Mov Disord* 1999;14(4):652–657.
32. Burbaud P, Guehl D, Lagueny A, et al. A pilot trial of clozapine in the treatment of cervical dystonia. *J Neurol* 1998;245(6–7):329–331.
33. Wolf M, Mosnaim A. Improvement of axial dystonia with the administration of clozapine. *Int J Clin Pharmacol Ther* 1994;32: 282–283.
34. Thiel A, Dressler D, Kistel C, et al. Clozapine treatment of spasmodic torticollis. *Neurology* 1994;44:957–958.