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CASE REPORT

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Serotonin syndrome caused by escitalopram in Parkinson's disease psychosis: a case report

Shan'mei Wang[1†], Linghe Qiu[1†], Qin Zhou[1], Caixia Chen[1*] and Jianhong Wu[1*]

Abstract

Background Serotonin syndrome and Parkinson's disease (PD) are two diseases whose symptoms partially overlap; this poses challenges in distinguishing them in clinical practice. Early manifestations such as tremor, akathisia, diaphoresis, hypertonia and hyperreflexia are common in mild-to-moderate serotonin syndrome and can also occur in PD. Without prompt recognition and treatment, serotonin syndrome can rapidly progress, potentially leading to severe complications such as multiple organ failure within hours. Given their disparate treatment strategies, accurate clinical distinction is crucial for effective treatment. This case study explores a patient with serotonin syndrome triggered by escitalopram in the context of PD psychosis (PDP), providing insights into diagnosis and treatment planning.

Case presentation A 75-year-old Asian woman with a one-year history of PD, a two-month history of PDP, and a six-year history of depression presented with symptoms including hyperreflexia, tremor, hypertonia, impaired level of consciousness, and inappropriate behavior following a recent one-month adjustment in medication. Initially suspected of being drug-induced parkinsonism or worsening PD, therapeutic drug monitoring revealed warning levels of escitalopram. Subsequent diagnoses confirmed serotonin syndrome. This syndrome may result from increased cortical serotonin activity at the serotonin2A receptor due to dopamine and serotonin imbalances in PDP, compounded by increased dopamine-mediated serotonin release. Additionally, being an intermediate metabolizer of cytochrome P450 enzyme 2C19, the patient experienced excessive escitalopram accumulation, exacerbating her condition.

Conclusions This case underscores the critical need to differentiate between symptoms of serotonin syndrome and PD, particularly in manifestations like tremor and hypertonia. Careful consideration of receptor profiles in patients with PDP is essential when selecting antidepressants to mitigate the risk of serotonin syndrome.

Keywords Parkinson's disease psychosis, Serotonin syndrome, Escitalopram, Case report

Background

Serotonin syndrome is a rapidly progressing and potentially life-threatening adverse drug reaction triggered by serotoninergic medications. It arises from excessive activation of postsynaptic serotonin receptors, manifesting in symptoms affecting both the central and peripheral nervous system [1]. Typical clinical features include an altered mental state, autonomic dysfunction, and neuromuscular excitement [2]. Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, tremors, and changes in gait and posture reflexes [3]. Early-stage serotonin syndrome symptoms, such as tremor and hypertonia, partially overlap with PD manifestations, posing significant challenges in clinical differentiation [4]. Herein, we report the case of a patient with PD psychosis (PDP) who was undergoing treatment with

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escitalopram and was subsequently diagnosed with serotonin syndrome. This report highlights the differences between serotonin syndrome and PD, emphasizing the use of therapeutic drug monitoring (TDM) and genetic testing to elucidate possible pathogenic mechanisms.

Case presentation

The patient was a 75-year-old woman with a six-year history of depression and a two-month history of PDP. On July 14, 2023, she was admitted to the hospital due to visual hallucinations and inappropriate behavior. Upon admission, the patient began treatment with levodopa/benserazide 0.125 g tid and quetiapine 12.50 mg qn. Three days later (July 17), in response to recurring depressive symptoms, escitalopram 5 mg qd was added to her regimen based on her medication history. The dosage of levodopa/benserazide was gradually reduced to 0.0625 g bid and quetiapine increased to 37.5 mg qn to manage persistent hallucinations and inappropriate behavior by July 19.

After a 12-day hospitalization (July 25), the patient reported no further hallucinations but continued to exhibit impaired insight and inappropriate nighttime behavior. Consequently, the dosage of quetiapine was reduced to 25 mg qn. To address persistent depression, escitalopram was gradually increased to 20 mg qd by July 28. On August 7, levodopa/benserazide was adjusted to 0.0625 g tid for bradykinesia.

However, by day 26 (August 8), the patient had developed impaired level of consciousness and alteration in language. As a result, the dosages of quetiapine and escitalopram were reduced to 12.5 mg qn and 10 mg qd, respectively. Two days later (August 10), she exhibited apathy, a slight neck tilt, sialorrhea, and urinary incontinence. Vital signs were: blood pressure 146/80 mmHg, heart rate 89 beats/minute, respiratory rate 18 breaths/minute, and temperature 36.3 °C. A physical examination revealed hypertonia and mild tremors. During the mental status examination, the patient exhibited impaired level of consciousness, disorientation, and a lack of cooperation. Laboratory tests showed no significant abnormalities, and a head scan indicated no changes from the initial admission.

Initially diagnosed with drug-induced parkinsonism (DIP), treatment included intravenous infusions of vitamins C and B_6, potassium chloride, and benzhexol 2 mg qd (Fig. 1). Despite treatment, her symptoms of hypertonia, tremors, hyperreflexia, neck stiffness, and neck tilt persisted over the next 24 h. Quetiapine levels measured 11.9 ng/ml, which was below the therapeutic range.

On August 11, the dosage of benzhexol was adjusted to 1 mg tid, and escitalopram was reduced to 5 mg qd. Three days later (August 14), the patient exhibited noticeable head tilting to the right and dysphagia. Persistent symptoms included tremors, limb stiffness, hyperreflexia, and hypertonia. Consequently, the dosage of benzhexol was increased to 2 mg bid and levodopa/benserazide to 0.125 g bid (Fig. 2).

This situation prompted the question: could this symptoms combination—autonomic dysfunction, neuromuscular excitement, and altered mental status—indicate serotonin syndrome, despite closely resembling the PD or DIP symptoms? To explore this possibility, we conducted TDM and genetic testing of escitalopram metabolic enzymes. Surprisingly, escitalopram levels measured 171.7 ng/ml, significantly exceeding the warning threshold. Genetic testing revealed a cytochrome P450 enzyme (CYP) 2C19 polymorphism, indicating intermediate metabolism. Based on these findings, the patient received a definitive diagnosis of serotonin syndrome.

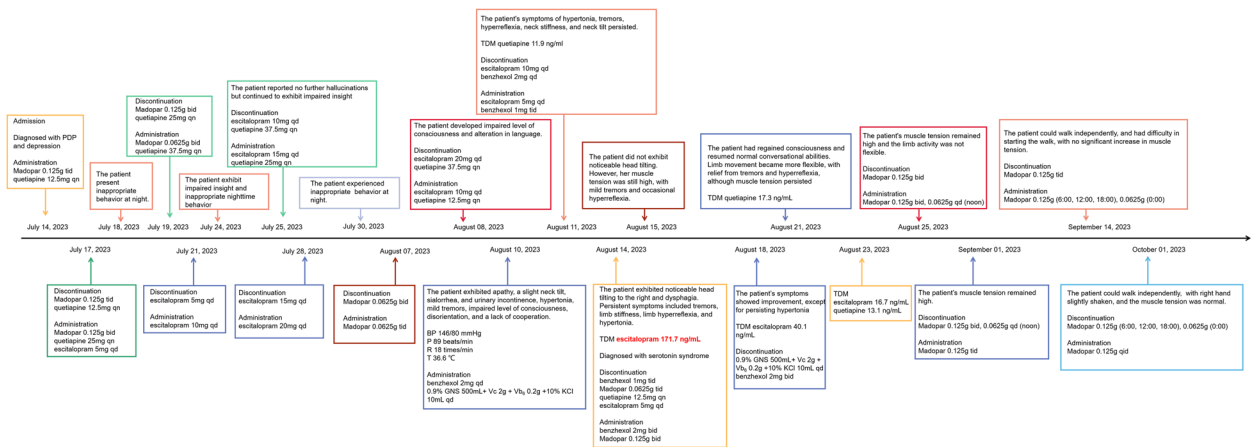

Fig. 1 Timeline of our patient

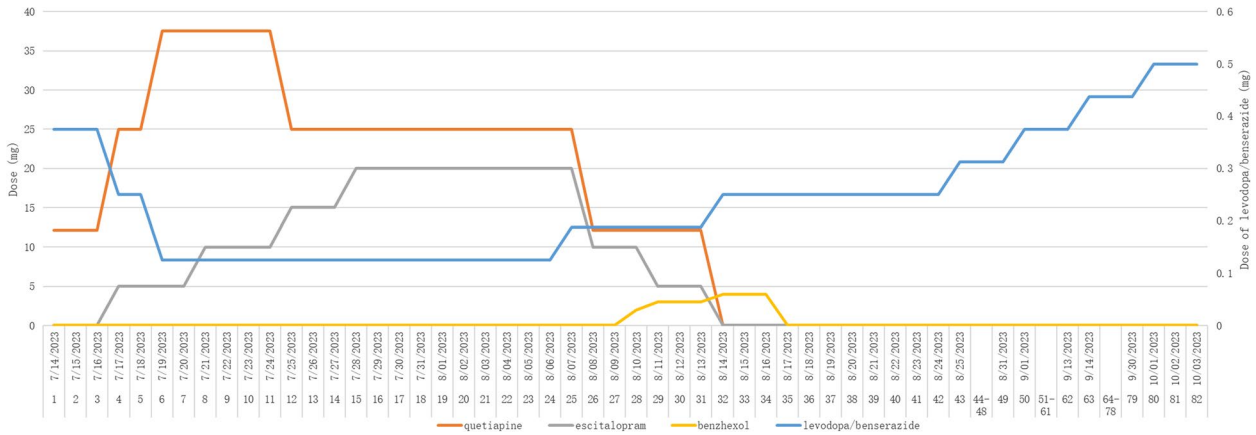

Fig. 2 Medication of quetiapine, escitalopram, benzhexol and levodopa/benserazide

Intravenous infusion therapy was continued to expedite drug metabolism, and both escitalopram and quetiapine were promptly discontinued. By August 18, with escitalopram levels reduced to 40.1 ng/ml, the patient's symptoms showed improvement, except for persisting hypertonia, prompting cessation of benzhexol and intravenous rehydration. By August 21, the patient had regained consciousness and resumed normal conversational abilities. Limb movement became more flexible, with relief from tremors and hyperreflexia, although muscle tension persisted, later confirmed as a symptom of PD. Over the subsequent months, levodopa/benserazide was gradually adjusted to 0.125 g qid. Muscle tension continued to improve, and the patient was discharged a few weeks after achieving stability.

Discussion and conclusions

According to Hunter's criteria, serotonin syndrome is characterized by well-defined symptoms including clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and elevated temperature (Fig. 3) [2]. The severity of these symptoms varies with serotonin toxicity severity and may not consistently appear in every patient [5]. Clonus, whether inducible, spontaneous, or ocular, is a core neuromuscular feature closely associated with serotonin syndrome [6]. However, not all patients exhibit obvious clonus; mild cases may only show tremor or an altered mental state, complicating the diagnosis.

Tremor and hypertonia can overlap with PD symptoms (Fig. 4). PD tremor, characterized by involuntary, rhythmic, alternating movements [7], typically presents as resting tremor [8]. In contrast, tremors associated with serotonin syndrome, or DIP, lack this re-emergent characteristic (Table 1). Hypertonia, an abnormal increase in muscle tone, can sometimes overshadow tremor [1, 9] and present in three forms: spasticity during passive movement, dystonia during active movement, and rigidity throughout all states of movement [10]. In serotonin syndrome, hypertonia appears as a neuromuscular excitation symptom, whereas PD-related rigidity stems from muscle weakness and impaired muscle flexibility [11]. Early-stage serotonin

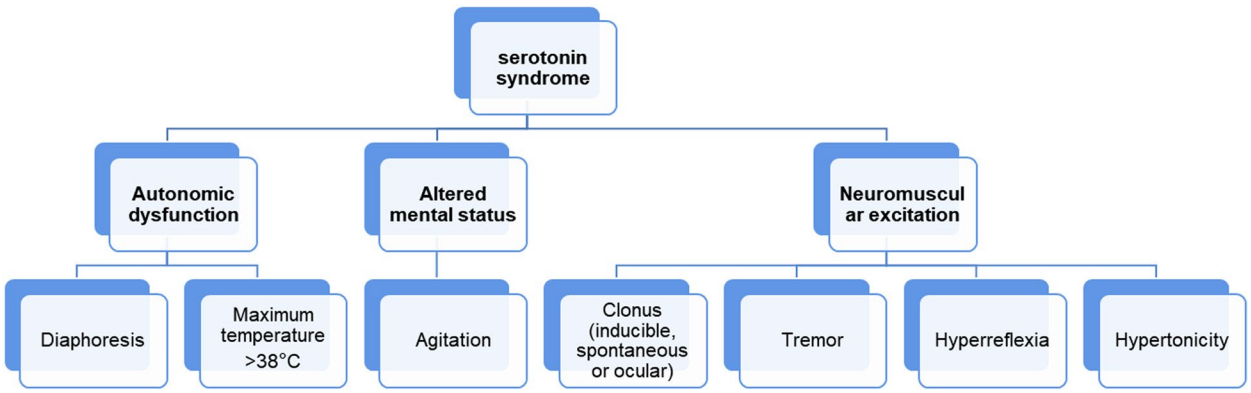

Fig. 3 Well-defined symptoms of serotonin syndrome

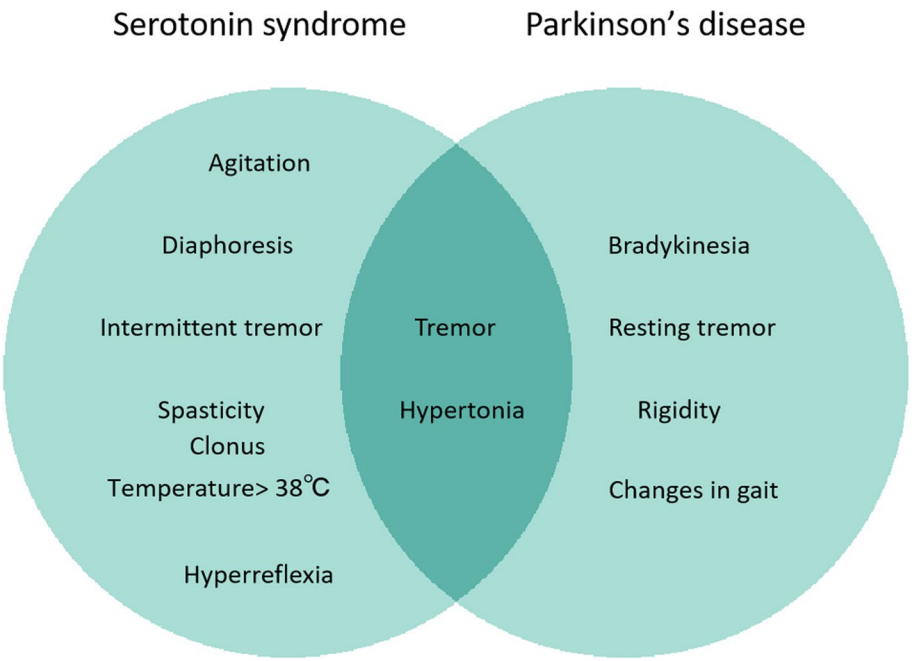

Fig. 4 Comparison of serotonin syndrome and PD

Table 1 Different types of tremors between PD, serotonin syndrome, neuroleptic malignant syndrome (NMS), DIP, and antidepressants induced-tremor

Classification	Type of tremor	Feature	Distinguish method
PD	resting tremor	appears when gravity is completely opposed, commonly unilateral in onset [12]	setting a new posture, such as holding hands flat. With a new posture, re-emergent tremor reappears after a few seconds, while other tremors appears immediately [13]
	re-emergent tremor	resting tremor ceases when the muscles are activated voluntarily to execute a posture, and it may be followed by delayed re-emergence of tremor when a new limb posture is sustained [14]	
Serotonin syndrome	intermittent tremor	greater in lower extremities [1]	
NMS	cogwheel tremor	lead tube rigidity in all muscle groups [15]	
DIP	essential tremor	a postural tremor and an action tremor [16, 17]	
Antidepressants induced-tremor			

syndrome, especially with mild neuromuscular excitement, may not exhibit clonus, posing challenges in differentiation from PD-induced rigidity.

To differentiate between spasticity and rigidity, a slow stretch of a muscle was performed, such as passively and slowly straightening the elbow joint from the flexed position. Spasticity does not manifest during slow stretching, whereas rigidity, characterized by continuous resistance akin to a lead pipe or cogwheel, remains consistent regardless of stretch speed. Notably, muscle symptoms in serotonin syndrome may be more prominent in the lower extremities compared to the upper extremities, providing a slight distinction in identifying these conditions (Table 2).

Our patient presented with hypertonia, tremor, and hyperreflexia, with particularly notable hyperreflexia observed during periods of elevated escitalopram levels, a typical symptom of serotonin syndrome [9]. Despite adjustments to levodopa/benserazide dosage, the tremor did not improve, ruling out the possibility of PD-induced tremor. Based on the elevated escitalopram levels and adherence to Hunter's criteria, the patient received a diagnosis of serotonin syndrome. Hypertonia persisted beyond the resolution of serotonin syndrome

Table 2 Different types of hypertonia between PD and serotonin syndrome

Classification	Type of hypertonia	Type of stretch reflection	Conduction path	Feature	Location	Special expression	Distinguish method
PD	rigidity [3]	non-speed dependent	extrapyramidal system	hypertonia present in all states of passive and active movement [18]	obvious in the flexors of the neck, trunk and limbs	lead tube rigidity and cogwheel rigidity	slowly stretch a muscle
Serotonin syndrome	spasticity (increased muscle tension caused by neurological lesions [19])	velocity-dependent hypertonia caused by upper motor neuron damage [20]	pyramidal system	muscle overactivity, hyperreflexia, clonus (rapid muscle contractions [19, 21]), clasp-knife phenomenon, flexor and extensor spasms, Babinski sign, and spastic dystonia [20].	obvious in the lower extremities [1]	clonus (inducible, spontaneous or ocular)	

Table 3 Differences between PD, serotonin syndrome, NMS, DIP, and malignant syndrome in PD

	Classification	Pathogenesis	Core symptoms	Treatment
Disease	PD	a neurodegenerative disease caused by dysfunction of the basal ganglia	bradykinesia, rigidity (hypertonia), tremor, and altered gait and postural reflexes [3]	pharmacologic approaches (typically with levodopa preparations prescribed with or without other medications) and nonpharmacologic approaches (such as exercise and physical, occupational, and speech therapies) [22]
Adverse drug reaction	serotonin syndrome	serotonin overdose in synaptic cleft	hyperreflexia, tremor, and clonus	intravenous hydration, general symptomatic treatment, withdrawal of the serotoninergic drugs and medication (cyproheptadine)
	NMS	a neuroleptic-induced alteration of central neuroregulatory mechanisms and an abnormal reaction of predisposed skeletal muscle [23]	hyperthermia (≥ 38.5℃), bradyreflexia [15, 24], muscle 'lead pipe' rigidity and an elevated creatine phosphokinase concentration	general symptomatic treatment, withdrawal of the neuroleptic agents and medication (bromocriptine and dantrolene)
	DIP	imbalance between dopamine and acetylcholine in the substantia nigra striatum	tremor, muscle rigidity, bradykinesia and loss of movement	withdrawal of antipsychotics, switch to other antipsychotics and medication (benzhexol)
Withdrawal reaction	malignant syndrome in PD	acute dopaminergic hypo-transmission in the hypothalamus, nigrostriatal system, and mesocortical dopaminergic system [25]	elevated serum creatine kinase, consciousness confusion, autonomic dysfunction, high temperature, and noticeable stiffness	intravenous hydration, external cooling, add levodopa, and medication (bromocriptine and dantrolene) [26]

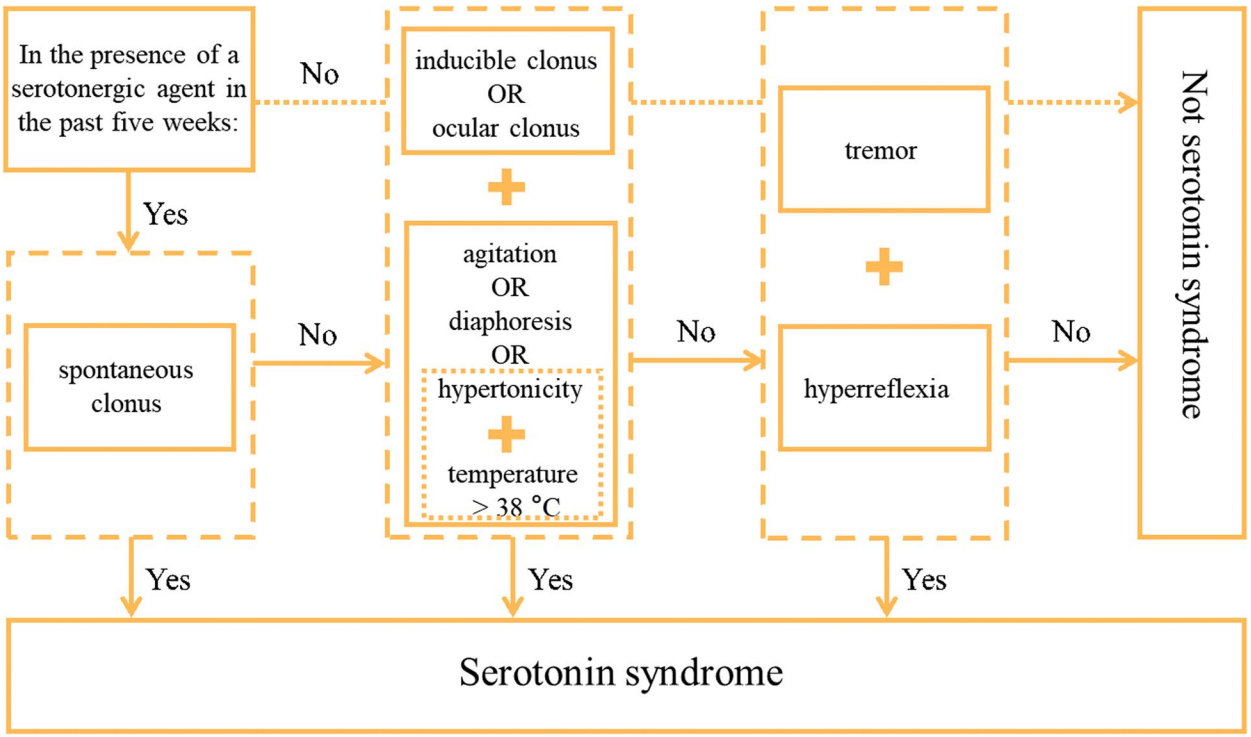

Fig. 5 The Hunter's decision rules of serotonin syndrome, adapted from Wu et al., 2023 [27]

but responded favorably to increased levodopa/benserazide, suggesting inadequate management PD symptoms. Despite considering various potential causes, including DIP, NMS, and malignant syndrome in PD, our diagnostic investigations did not support these alternative diagnoses (Table 3).

Serotonin syndrome, despite sharing similarities with other syndromes, can be readily diagnosed using Hunter's criteria (Fig. 5, adapted from Wu et al., 2023 [27]). It is crucial for clinicians treating PD patients to be vigilant about the potential association with serotonin syndrome. Once this connection is recognized, identifying clinical features and applying Hunter's diagnostic criteria simplifies the diagnostic process.

The development of serotonin syndrome in our patient had the following stages: the patient experienced visual hallucinations subsequent to the PD diagnosis, indicating PDP. More than 50% of PD patients progress to PDP [28], characterized by dopamine deficiency in the substantia nigra and striatum, along with excessive cortical serotonin and midbrain marginal dopamine. This imbalance amplifies serotonin-mediated neurotransmission in the lateral temporal cortex, which is crucial for visual processing, thereby precipitating hallucinations [29]. This phenomenon likely results from toxic alpha-synuclein-containing Lewy bodies depositing in the cerebral cortex, disrupting serotonin and dopamine neurotransmission, upregulating and overstimulating cortical serotonin2A receptors, and triggering excessive dopamine release in mesolimbic circuits [30]. Simply put, PDP can be conceptualized as a serotonin-dopamine imbalance syndrome, where heightened serotonin2A or dopamine2 receptor activity, or both [30], amplify the impact of increased synaptic serotonin due to heightened serotonin2A receptor activity. Moreover, escitalopram is primarily metabolized by CYP2C19, a highly polymorphic enzyme that introduces individual variations in pharmacokinetics [27]. Our patient, identified as an intermediate metabolizer with two nonfunctional alleles (CYP2C19 *1/*2), exhibited slower escitalopram metabolism, resulting in drug accumulation. Additionally, while levodopa typically reduces brain serotonin levels, it can also enhance serotonin release and undergo decarboxylation into dopamine within serotoninergic neurons. This process involves the translocation of endogenous serotonin to synaptic clefts and receptor sites [31]. Consequently, the combination of increased serotonin receptor activity, reduced serotonin reuptake due to escitalopram overdose, and increased serotonin release from levodopa collectively elevates serotonin levels, contributing to serotonin syndrome.

For PDP patients, blocking serotonin2A receptors theoretically reduces excessive serotonin levels, restores the serotonin-dopamine balance, and alleviates visual hallucinations without exacerbating motor symptoms.

Serotonin2A receptor blockers, reverse agonists, or antipsychotic drugs with serotonin2A antagonist effects are used to manage psychiatric symptoms [28]. However, in treating depression in PDP patients, up-regulation of serotonin receptors theoretically increases the risk of serotonin syndrome when using selective serotonin reuptake inhibitors.

This study represents the first comparison of neurological manifestations between PD and serotonin syndrome. Early-stage of serotonin syndrome symptoms may be obscured by PD, especially in the absence of core symptoms. Identifying symptoms such as tremors is crucial for distinguishing between PD and serotonin syndrome. Hypertonia may be more challenging to differentiate and should be assessed based on medication history and a physical examination. Core symptoms of serotonin syndrome, including hyperreflexia and clonus, facilitate rapid diagnosis when coupled with medication records, which should be closely monitored in clinical settings. TDM and genetic testing are sometimes necessary for managing serotonin syndrome effectively.

Abbreviations

NMS	Neuroleptic malignant syndrome
PD	Parkinson's disease
PDP	Parkinson's disease psychosis
DIP	Drug-induced parkinsonism
TDM	Therapeutic drug monitoring
CYP	Cytochrome P450 enzyme

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Authors' contributions
JW and SW gathered the information; LQ and QZ performed the literature search; CC analyzed the data, and coordinated the case report; JW contributed to writing the first draft of the manuscript, and LQ edited and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The patient signed an informed consent form to receive hospital care and to authorize the use of personal health information for academic purposes. The informed consent form is archived at The Affiliated Mental Health Center of Jiangnan University. Wuxi, China, together with the medical record. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of The Affiliated Mental Health Center of Jiangnan University (WXMHCIRB2023LLky007).

Consent for publication
Informed consent was obtained from the patient and her legal guardian(s) for publication of clinical information, and information has been de-identified to protect anonymity. The informed consent form is archived at The Affiliated Mental Health Center of Jiangnan University. Wuxi, China, together with the medical record.

Competing interests
The authors declare no competing interests.

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References

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112–20.
2. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96(9):635–42.
3. Ye H, Robak LA, Yu M, Cykowski M, Shulman JM. Genetics and pathogenesis of Parkinson's syndrome. Annu Rev Pathol. 2023;18:95–121.
4. Wang RZ, Vashistha V, Kaur S, Houchens NW. Serotonin syndrome: preventing, recognizing, and treating it. Clevel Clin J Med. 2016;83(11):810–7.
5. Mikkelsen N, Damkier P, Pedersen SA. Serotonin syndrome-A focused review. Basic Clin Pharmacol Toxicol. 2023;133(2):124–9.
6. Gillman PK. The serotonin syndrome and its treatment. J Psychopharmacol. 1999;13(1):100–9.
7. Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. Nat Rev Neurol. 2010;6(1):29–37.
8. Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain. 2012;135(Pt 11):3206–26.
9. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. BMJ. 2014;348:g1626.
10. Evans SH, Cameron MW, Burton JM. Hypertonia. Curr Probl Pediatr Adolesc Health Care. 2017;47(7):161–6.
11. Monte A, Magris R, Nardello F, Bombieri F, Zamparo P. Muscle shape changes in Parkinson's disease impair function during rapid contractions. Acta Physiol (Oxf). 2023;238(1):e13957.
12. Leodori G, Belvisi D, De Bartolo MI, Fabbrini A, Costanzo M, Vial F, Conte A, Hallett M, Berardelli A. Re-emergent Tremor in Parkinson's disease: the role of the motor cortex. Mov Disord. 2020;35(6):1002–11.
13. Jankovic J, Schwartz KS, Ondo W. Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;67(5):646–50.
14. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.
15. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am. 1993;77(1):185–202.
16. Friedman JH. Movement disorders induced by psychiatric drugs that do not block dopamine receptors. Parkinsonism Relat Disord. 2020;79:60–4.
17. Arbaizar B, Gómez-Acebo I, Llorca J. Postural induced-tremor in psychiatry. Psychiatry Clin Neurosci. 2008;62(6):638–45.
18. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics. 2003;111(1):e89-97.
19. Wieters F, Weiss Lucas C, Gruhn M, Büschges A, Fink GR, Aswendt M. Introduction to spasticity and related mouse models. Exp Neurol. 2021;335:113491.
20 Sheean G. The pathophysiology of spasticity. Eur J Neurol. 2002;9 Suppl 1:3–9. dicussion 53-61.
21. Gracies JM, Bayle N, Vinti M, Alkandari S, Vu P, Loche CM, Colas C. Five-step clinical assessment in spastic paresis. Eur J Phys Rehabil Med. 2010;46(3):411–21.
22. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2020;323(6):548–60.
23. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth. 2000;85(1):129–35.
24. Prakash S. A diagnostic confusion between Serotonin syndrome and Neuroleptic malignant syndrome. Am J Emerg Med. 2021;43:272–3.

25. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism Relat Disord. 2003;9(Suppl 1):S3-9.
26. Yamawaki Y, Ogawa N. Successful treatment of levodopa-induced neuroleptic malignant syndrome (NMS) and disseminated intravascular coagulation (DIC) in a patient with Parkinson's disease. Intern Med. 1992;31(11):1298–302.
27. Wu J, Yu J, Qu K, Yin J, Zhu C, Liu X. Serotonin syndrome caused by a CYP2C19-mediated interaction between low-dose escitalopram and clopidogrel: a case report. Front Psych. 2023;14:1257984.
28. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383(9916):533–40.
29. Huot P, Johnston TH, Darr T, Hazrati LN, Visanji NP, Pires D, Brotchie JM, Fox SH. Increased 5-HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations. Mov Disord. 2010;25(10):1399–408.
30. Stahl SM. Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. CNS Spectr. 2016;21(5):355–9.
31. Everett GM, Borcherding JW. L-dopa: effect on concentrations of dopamine, norepinephrine, and serotonin in brains of mice. Science. 1970;168(3933):849–50.

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