

Association Between Lower Extremity Edema and Risperidone in an Older Adult

Shuo Qiu, MD; Darlon Jan, MD; and Kye Y. Kim, MD

A number of case reports have been reported on induction of lower extremity edema by risperidone; however, the risk factors and pathophysiology are not well elucidated.¹⁻³ This case report highlights the bilateral lower extremity edema in an older person in a long-term care setting. We also propose several additional risk factors that resulted in her edema.

Case Report

Ms A, a 71-year-old married woman, was seen with her daughter for an approximately 9-year gradual decline in memory. She had no prior history of psychiatric disorder, but her family history was significant for alcoholism (father). Ms A had multiple chronic medical conditions, such as gastroesophageal reflux disease, hypertension, type 2 diabetes mellitus, osteoarthritis, sleep apnea, and others. At the initial visit, she denied any memory trouble, but she scored 8/30 on the Montreal Cognitive Assessment⁴ and 2/15 on the Geriatric Depression Scale⁵ while she was alert and fully awake. Her medical dementia workup was negative for reversible causes of memory dysfunction. Her treatment was initially focused on trials of antidementia medications and family education. She could not tolerate donepezil due to persistent diarrhea. Subsequently, she was placed on memantine and titrated up to 10 mg 2 times/d without noticeable adverse reactions. Despite starting memantine, her cognitive functions progressively worsened, and she began experiencing visual hallucinations of seeing people in her room and delusions of her husband having extramarital affairs. Additionally, her mood instability became significant and frequent. The patient was eventually placed on quetiapine for her worsening psychotic symptoms, which was titrated to 25 mg at bedtime. However, she became more confused, unstable in gait, and started falling. It was discontinued and changed to risperidone. Her visual hallucinations rather quickly responded to 0.5 mg/d, but her delusions and mood instability gradually improved on 0.5 mg 2 times/d. She began showing positive outcomes to this medication, but her family noted that her lower legs were swollen up to both knees. No pain was associated with this change but measured as > 2 pitting edema. Per her family's request, risperidone was discontinued, and the edema resolved over a period of 2 weeks. No recurrence was noted at the next follow-up visit. Based on her existing medical conditions and all laboratory data, no clear-cut physical cause for the edema was found. In terms of treating her psychotic symptoms, she was switched back to quetiapine as needed for intermittent agitation per her family's request.

Discussion

This case measured on the Naranjo scale⁶ was a "probable" association between risperidone and lower leg edema. Using the Naranjo scale, the association between risperidone and lower extremity edema was measured to be 5, corresponding to a probable association. This means that the edema follows a reasonable temporal sequence after the introduction of risperidone. Further association was established when the edema resolved after stopping risperidone. Since the exact mechanism of how risperidone causes edema is unknown, it is important to be mindful of this potential side effect and its risks factors. Risk factors reported in the literature include older age and coadministration with psychiatric medications such as citalopram.^{1,7,8} Additional studies are needed to quantify the risk of older age and coadministration of certain psychiatric medications. Proposed mechanisms include sensitizing α -1 receptors, downregulating adenosine triphosphate-dependent calcium pump, and altering renal function, all of which contribute to peripheral edema.^{1,7,8} Edema generally resolves after lowering the dose of or discontinuing risperidone.^{1,3} Some case reports allude to the dose-dependent nature of edema risk.^{1,9} Another potential risk factor for edema caused by risperidone is medications that inhibit metabolism of risperidone, mainly cytochrome P450 (CYP) 2D6 inhibitors. This patient was also taking memantine, which is a known CYP2D6 inhibitor.¹⁰ Risperidone is metabolized by CYP2D6.¹¹ As a result, the edema-inducing mechanism of risperidone is amplified by memantine. Lastly, it is possible that her inadequate glucose control contributed to her edema.

Risperidone is not the only antipsychotic implicated in the induction of lower extremity edema. Other antipsychotics implicated are quetiapine, haloperidol, olanzapine, and ziprasidone.^{2-5,7,12} Based on other case reports,^{1,7,8} aripiprazole does not induce edema in patients who previously reacted to risperidone, possibly due to differences in pharmacodynamics. Our patient did not develop edema while taking quetiapine. Patients who react to one antipsychotic should be tried on another antipsychotic, preferably with a different mechanism of action.

This case report highlights the importance of monitoring for lower extremity edema in the geriatric population exposed to antipsychotics. For reasons still under investigation, risperidone increases the risk of lower extremity pitting edema. Our patient's risk was compounded by diabetes and hypertension, both of which are common comorbidities in the geriatric population. However, our patient's induced edema resolved by stopping risperidone.

Article Information

Published Online: August 3, 2023. <https://doi.org/10.4088/PCC.22cr03414>

© 2023 Physicians Postgraduate Press, Inc.

Prim Care Companion CNS Disord 2023;25(4):22cr03414

Submitted: September 8, 2022; accepted January 13, 2023.

To Cite: Qiu S, Jan D, Kim KY. Association between lower extremity edema and risperidone in an older adult. *Prim Care Companion CNS Disord*. 2023;25(4):22cr03414.

Author Affiliations: Department of Psychiatry and Behavioral Medicine, Virginia Tech Carilion School of Medicine and Carilion Clinic Center for Healthy Aging, Roanoke (Qiu, Jan, Kim).

Corresponding Author: Kye Y. Kim, MD, Carilion Clinic Center for Healthy Aging, 2001 Crystal Springs Ave, Suite 302, Roanoke, VA 24014 (kykim@carilionclinic.org).

Relevant Financial Relationships: None.

Funding/Support: None.

Additional Information: Patient information has been de-identified to protect anonymity.

REFERENCES

1. Liu LY, Hsu CC. Risperidone-associated edema. *Am J Ther*. 2020;27(6):e667–e669.
2. Munshi S, Mukherjee S, Saha I, et al. Pedal edema associated with atypical antipsychotics. *Indian J Pharmacol*. 2016;48(1):88–90.
3. Soumya RN, Grover S, Dutt A, et al. Angioneurotic edema with risperidone: a case report and review of literature. *Gen Hosp Psychiatry*. 2010;32(6):646.e1–646.e3.
4. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699.
5. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982–1983;17(1):37–49.
6. Seger D, Barker K, McNaughton C. Misuse of the Naranjo Adverse Drug Reaction Probability Scale in toxicology. *Clin Toxicol (Phila)*. 2013;51(6):461–466.
7. Yang HN, Cheng YM. Peripheral edema associated with risperidone oral solution: a case report and a review of the literature. *J Clin Psychopharmacol*. 2012;32(1):128–130.
8. Hosseini SH, Ahmadi A. Peripheral edema occurring during treatment with risperidone combined with citalopram. (Internet) *Case Rep Med*. 2012;2012:540732.
9. Ravasia S. Risperidone-induced edema. *Can J Psychiatry*. 2001;46(5):453–454.
10. Micuda S, Mundlova L, Anzenbacherova E, et al. Inhibitory effects of memantine on human cytochrome P450 activities: prediction of in vivo drug interactions. *Eur J Clin Pharmacol*. 2004;60(8):583–589.
11. Dean L. Risperidone therapy and CYP2D6 genotype [Internet], in Medical Genetics Summaries. Pratt VM, Scott SA, Pirmohamed M, et al, eds. Bethesda (MD), National Center for Biotechnology Information (US). 2012. NIH website. Accessed June 12, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK425795/>
12. Umar MU, Abdullahi AT. Self-limiting atypical antipsychotics-induced edema: clinical cases and systematic review. *Indian J Psychol Med*. 2016;38(3):182–188.