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Risperidone-induced angioedema

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Abstract

Risperidone is a second-generation antipsychotic with common adverse effects, such as extrapyramidal symptoms, weight gain, hyperprolactinemia, and sedation. Angioedema, although generally considered to be uncommon, has previously been documented to occur following administration of some antipsychotics, including risperidone. This report describes a case of risperidone-induced angioedema in an older male patient.

Keywords: risperidone, angioedema, adverse drug effect

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Background

Risperidone is a second-generation antipsychotic available in tablet, oral solution, orally disintegrating tablet, and long-acting injectable formulations.[1-3] It has FDA approval for the treatment of schizophrenia in adults and adolescents; as monotherapy or in combination with lithium or valproate for the treatment of acute mania or mixed episodes associated with bipolar I disorder in adults, adolescents, and children; and irritability associated with autism spectrum disorder in adolescents and children.[1] Common adverse effects of risperidone include extrapyramidal symptoms, weight gain, hyperprolactinemia, and sedation.[4] Angioedema secondary to risperidone use is an uncommon reaction with unreported frequency based on package insert data.[1-3] Another less common side effect of risperidone is QTc prolongation.[4]

Angioedema is self-limiting swelling that can have allergic and nonallergic etiologies and can involve the mucosa, submucosa, or subcutaneous tissues and may last several days.[5,6] It tends to affect areas with loose connective tissue, such as the face, lips, mouth, throat, larynx, uvula, extremities, and genitalia. It can be life-threatening when it involves the respiratory tract.[6] Drug-induced angioedema can also be classified into allergic and nonallergic types, and they differ in their pathogenesis, presentation, and management.[7] Drug-induced allergic angioedema is a type I hypersensitivity mediated by histamine through mast cell activation. It presents with a rapid onset of swelling, usually within 1 to 6 hours and commonly with an urticarial rash. Due to its pathogenesis, it responds well to antihistamine, epinephrine, and corticosteroid treatment.[6,7] This type of angioedema is suspected if it appears temporally related to an exogenous stimulus. It may be confirmed by a positive skin prick test and/or detection of stimulus-specific immunoglobulin E.[6]

Drug-induced nonallergic angioedema, on the other hand, mediated by bradykinin, tends to lack the presence of an urticarial rash. It is asymmetrical and nonpitting and appears in a more gradual manner after a few hours to 2 days after exposure to the stimulus. It does not respond well to antihistamines, epinephrine, or corticosteroid treatment; therefore, recommended management is primarily discontinuing the offending agent.[5,7] This type of angioedema occurs on a hereditary or acquired basis due to a C1 inhibitor (C1-INH, a component of the complement system) deficiency.[5] The complement system plays an important role in immunology and inflammation by targeting antigens for phagocyte

TABLE 1: Types of drug-induced angioedema

	Allergic	Nonallergic
Pathological mediators	Histamine	Bradykinin
Clinical presentation	Symmetrical swelling, urticaria	Asymmetrical, nonpitting swelling
Confirmation tests	• Skin prick test • Clinically significant levels of immunoglobulin E	Decreased levels of C1 inhibitor
Onset	Within 1 to 6 hours of exposure	Gradually, hours to days after exposure
Treatment	Antihistamines, epinephrine, corticosteroids	Discontinuation of offending agent, supportive care if respiratory tract is involved
Time to resolution of symptoms after treatment	Within 24 hours	Within 5 days

consumption. A deficiency in C1-INH can result in the dysregulation of bradykinin production, which increases vascular permeability and leads to angioedema. Previous case reports of risperidone-induced angioedema have hypothesized that risperidone may suppress C1-INH activity as evidenced by decreased serum concentrations of C1-INH found after the angioedema occurred.[8,9] For a summary of the 2 types of drug-induced angioedema, please refer to Table 1.

At this time, only 10 cases listing risperidone as the only probable causative agent for angioedema have been reported to the FDA based on FDA Adverse Event Reporting System Public Dashboard data, which comprises reports from 1969 to the present day.[10] The following case describes a patient in the United States who experienced facial swelling after exposure to risperidone.

Case Report

An 80-year-old male recently admitted to a long-term care facility was observed by nursing staff to have new onset facial swelling. His medical history was significant for bipolar disorder, dementia (presumed to be vascular), cerebrovascular accident, atrial fibrillation, hyperlipidemia, hypothyroidism, and benign prostatic hyperplasia. Swelling onset was noted during olanzapine to risperidone cross-taper (starting dose 0.25 mg twice daily), which was initiated due to olanzapine inefficacy and prior benefit with risperidone reported in the past. He was also prescribed amlodipine 5 mg by mouth daily, atorvastatin 20 mg by mouth daily, carvedilol 25 mg by mouth twice daily, cholecalciferol 50 mcg by mouth daily, docusate 200 mg by mouth daily, furosemide 20 mg by mouth daily, levothyroxine 75 mcg by mouth daily, melatonin 9 mg by mouth at bedtime, potassium chloride 20 mEq by mouth daily, rivaroxaban 20 mg by mouth daily, senna 17.2 mg by mouth daily, tamsulosin 0.4 mg by mouth at bedtime, valproic acid oral solution 750 mg by mouth twice daily, tramadol 50 mg by mouth twice daily, and trazodone 25 mg by mouth at bedtime. Of note, 2 months prior to this presentation, the patient was treated for an upper body rash with topical hydrocortisone and ammonium lactate lotion. The rash was deemed to be secondary to lisinopril, and no recurrence of rash was reported following discontinuation of lisinopril.

Approximately 15 hours following the first dose of risperidone, nursing staff reported possible facial swelling. Vital signs were taken at that time: blood pressure 132/68 mmHg, heart rate 80 bpm, and oxygen saturation 96% on room air. Nine hours later, nursing staff noted worsened edema on the right side of the patient's face and jaw. Vital signs were taken again with unremarkable results. Less than 1 hour later, nursing staff alerted the on-call clinician for persistent swelling. The on-call physician ordered 1 dose of prednisone 20 mg by mouth until the patient could be fully evaluated the following morning. Overnight, staff continued to document the progression of swelling on the right side of the patient's face and his right hand. Early the next morning and 33 hours after the first dose of risperidone was given, the edema was noted to have spread to both orbital areas, and the patient was unable to open his eyes. Right ear and lip involvement was reported by staff at the time of nurse practitioner arrival for evaluation 3 hours later. Progression was also noted to the left side of the face, however, to a less severe degree. Clinician's evaluation noted bilateral periorbital edema, general facial edema with right-side prominence, and involvement of lips. No rash or hives were noted. The patient remained unable to open his eyes, and slight salivation was noted. No other symptoms were noted at that time. He was deemed alert with mild confusion, which was not significantly different from his baseline. Emergency medical services was called, and the patient was transferred to the local emergency department for further evaluation and treatment. At time of transfer to the outside facility, the patient had received a total of 3 doses of risperidone 0.25 mg.

Of note, the patient had previously been prescribed risperidone (up to 2 mg/day) with no issues reported. Active prescriptions from 2006 to 2011 show irregular fill histories, which likely correlate with intermittent adherence. At that time, he was also prescribed carbamazepine by psychiatry to manage his bipolar disorder. At the outside hospital, risperidone was discontinued, and the patient received methylprednisolone and diphenhydramine with other routine supportive care. He returned to the long-term care unit 2 days later in stable condition.

Discussion

This case adds to the few existing reports of risperidone-induced angioedema.[7,8,12-16] Angioedema has been reported

TABLE 2: Naranjo scores of prior cases of risperidone-induced angioedema

Case	Patient(s)	Naranjo Score Provided[a]	Estimated Naranjo Score[a]
Cooney and Nagy[8]	30-year-old female	None	8
Samra et al[9]	40-year-old male	None	5
Gonzalez et al[12]	63-year-old female	6	—
	42-year-old male	7	
	50-year-old male	7	
Güneş et al[13]	55-year-old female	7	—
Soumya et al[14]	15-year-old male	6	—
Talaei et al[15]	38-year-old female	None	5
Kores Plesnicar et al[16]	63-year-old female	None	7

[a]Reaction considered definite if score 9 or above, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.

with other antipsychotics, including paliperidone, the active metabolite of risperidone.[17] Cross-reactivity between antipsychotics has also been documented, and this highlights the need for careful assessment of medication trials. This is particularly relevant between antipsychotics with similar chemical structures, such as lurasidone, ziprasidone, and risperidone; aripiprazole and brexpiprazole; and clozapine and olanzapine.[18,19]

Previous case reports have varied on time to onset of angioedema, presence of concomitant medications, history of prior tolerability, and the dose (range of 1 to 6 mg/day oral risperidone) and formulation implicated. This case aligns with the most recently reported case in 2018 in which angioedema developed in less than 24 hours and following the first dose of risperidone.[8] A Naranjo score for this case was calculated to be 7, suggesting a probable association between risperidone and angioedema.[11] A comparison of Naranjo scores from prior case reports is summarized in Table 2. For our case, previous clinician notes and medication fill history would suggest the patient had previously taken risperidone and tolerated it well, but there was no objective evidence available to confirm this.

The patient's angioedema was first treated as an allergic-type reaction with the usual treatment of corticosteroids and antihistamines; then, it was later treated as a nonallergic-type reaction, which involves discontinuation of the offending agent. As the patient's initial symptoms began 15 hours after the first dose, steadily progressed in symptom severity despite administration of prednisone, and no hives or rash developed, this case is more consistent with drug-induced nonallergic angioedema. However, as no immunologic labs were drawn and the patient's angioedema was noted to be bilateral, we cannot confirm or rule out a mixed-type reaction. Additionally, as the patient was prescribed multiple medications, it is possible that risperidone in combination with one or more of his medications could have unexpectedly precipitated this edema.

Conclusion

Although likely to be a rare complication of risperidone use, clinicians should remain aware of the potential risk of angioedema related to risperidone that may not be dose- or formulation-dependent. Underlying mechanisms for this reaction are not fully known at this time, but many theories exist. Immunologic lab work can aid in determining the type of reaction; however, the impact of these labs on clinical outcome may be minimal. Concern for cross-reactivity among antipsychotics has also been noted in the literature. Clinician awareness and monitoring is crucial to manage these types of reactions.

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