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CASE REPORT

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Risperidone induced angioedema with concurrent EPS symptoms: a case report and review of literature

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ABSTRACT

Angioedema has recently been reported as a side effect associated with the antipsychotic risperidone. We report a case of dystonia with concurrent angioedema due to risperidone. A 40-year-old male with a history of schizophrenia was started on 3 mg of risperidone BID and developed perioral and periorbital edema along with increased muscle rigidity and hand tremor within 24 h of initial administration. His symptoms abated after cessation of risperidone and intravenous administration of corticosteroids and antihistamine. This case study adds to the current literature, which has already established angioedema as a dose-dependent side effect of risperidone. Moreover, this case study aims to increase awareness about the potential for the simultaneous occurrence of angioedema and extrapyramidal symptoms, and promotes vigilance among prescribers so that the life-threatening consequences of such effects can be avoided.

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1. Introduction

Risperidone is a psychotropic agent that is a benzisoxazole derivative. Risperidone's therapeutic activity is mediated through its dopamine type 2 (D2) and serotonin type 2 (5HT2) receptor antagonism. This drug is a widely prescribed agent that has been effective in ameliorating the symptoms of schizophrenia, bipolar disorder, autism, Tourette's syndrome, dementia, and delirium [1]. Typically, clinicians utilize risperidone to address the symptoms of psychosis, hyperactivity, irritability, and aggressiveness. Weight gain, extrapyramidal side effects, and sedation have been reported as adverse effects of risperidone [1].

Angioedema is an adverse effect seen in patients taking risperidone, as described in recent case reports by Cooney 1995, Kores 2001, and Soumya 2010 [2–4]. Angioedema is an abrupt swelling of skin, mucous membranes, and/or both which can include the upper respiratory and gastrointestinal tracts. Swelling of the tongue, larynx, and pharynx can potentially be life threatening by compromising the airway. Lip and periorbital swelling are the most common sites for angioedema to occur [5]. Though a wide range of medications have been found to cause angioedema, the angiotensin-converting enzyme inhibitors are the most frequently reported. A comprehensive literature review was conducted, searching for reports of risperidone-induced angioedema along with the concomitant occurrence of extrapyramidal symptoms and angioedema.

2. Case report

40-year-old male with a history of paranoid schizophrenia, depression, sarcoidosis, and recurrent psychiatry admissions presented to the emergency department (ED) with a 3-day history of lip swelling and increasing stiffness in upper and lower limbs (Figure 1). Patient had been recently discharged on risperidone for suicidal ideation prior to this ED visit. After taking his first dose in the evening, he woke up with lip swelling the next morning and also noted increasing limb stiffness, which precluded ambulation. He did not take an additional doses and decided to visit to the ED because his symptoms did not resolve after 3 days. He denied difficulty swallowing, SOB, chest pain, wheezing, weakness, numbness, tingling, visual or speech changes.

On physical examination, his vital signs were stable, without evidence of impending airway obstruction: temperature 36.9°C, heart rate 78, respiratory rate 15, blood pressure 121/77, SpO2 97% on room air, and weight of 77.1 kg. He had normal effort of breathing without stridor, wheezing, accessory muscle use, or respiratory distress upon presentation. There were no swallowing difficulties. He was noted to have facial stiffness, upper and lower lip swelling, inability to open his jaw, and abnormal muscle tone of 3+ in the upper and lower limbs. He was alert and oriented to person, place, and time.

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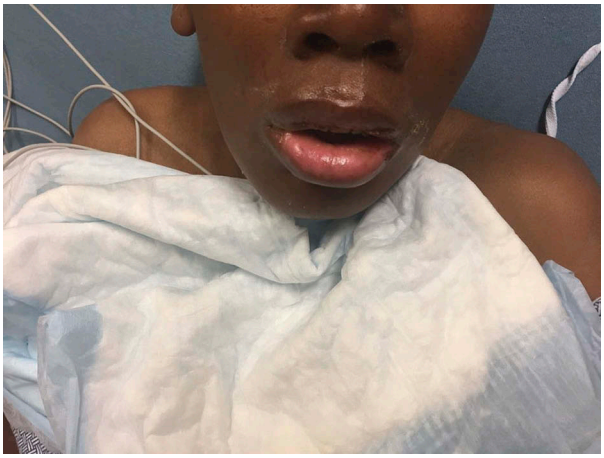

Figure 1. Angioedema of lips noted on admission in ED. Photograph was printed with patient's permission.

Laboratory testing showed deranged renal indices and elevated creatinine kinase levels, as listed in Tables 1–3. He was commenced on intravenous diphenhydramine, methylprednisone, and crystalloid. Risperidone was withheld, without replacement therapy. Progressive resolution in angioedema, dystonia, and acute kidney injury ensued over the next day. By day 3 of the admission, the patient was able to ambulate and have full use of his limbs. His psychiatrist was consulted, and he was commenced the patient on quetiapine at the time of discharge.

Levels of complements (C3, C4) and C1 esterase inhibitor, which were drawn on admission, were subsequently noted to be within the normal range. The patient has been followed up in clinic over the ensuing six months and has had no recurrence of symptoms since cessation of the likely offending drug.

Social History: former smoker
Labs: On initial presentation
Hemoglobin: 11.1
Hematocrit: 31.9
Sodium: 153
BUN: 34
Creatinine: 1.64
AST: 124
Protein: 9.4
CK Total: 1468
C3: 82 mg/dl (normal 80-160mg/dl)
C4: 22 mg/dl (normal 16–48 mg/dl)
C1 esterase inhibitor: 18 mg/dl (normal 17-35mg/dl)

Imaging: Ct Head/Brain without Contrast
Impression: No evidence of acute intracranial pathology

Table 2. Lab values obtained over hospital course.

	10/13/16	10/12/16 0545	10/11/16 0531	10/10/16 1855
WBC	4.3	4.7	6.3	7.1
HEMOGLOBIN	10.3	9.7	9.6	11.1
HEMATOCRIT	30.3	28.5	28.3	31.9
PLATELETS	205	207	231	261

Table 3. Lab values obtained over hospital course.

	10/13/16	10/12/16 0545	10/11/16 2045	10/11/16 0531	10/10/16 2101
CK TOTAL	646	1025	1032	–	1468
TROPONIN I	–	–	–	<0.012	<0.012

3. Discussion

Risperidone is an atypical antipsychotic drug is found to be effective in treating schizophrenia, bipolar disorder, and behavioral problems including hyperactivity, aggressiveness, and irritability associated with autism [6]. The commonly described adverse effects include insomnia, agitation, anxiety, fatigue, and extrapyramidal symptoms, such as the acute dystonia as seen in our patient [7]. Angioedema, a rare side effect, was first reported in 1995 by Cooney et al. [2]. They reported a case of a 30-

Table 1. Lab values obtained over hospital course.

	10/13/16	10/12/16 0545	10/11/16 0531	10/10/16 2101	10/10/16 1855
SODIUM	141	140	141	–	153
POTASSIUM	3.7	3.5	3.7	–	4.3
CHLORIDE	109	109	109	–	107
CO2	25	24	22	–	22
ANION GAP	–	7	10	–	24
BUN	9	15	27	–	34
CREATININE	1.20	1.31	1.48	–	1.64
EGFR IF NON-AFRICAN AMERICAN	–	>60	53	–	47
EGFR IF AFRICAN AMERICAN	–	>60	>60	–	57
GLUCOSE BLD	90	95	79	–	75
CALCIUM	9.1	8.8	8.8	–	9.6
MAGNESIUM	–	–	–	2.1	–
TOTAL PROTEIN	–	7.3	7.7	–	9.4
ALBUMIN	–	3.6	3.9	–	4.7
AST	–	72	95	–	124
ALT	–	39	42	–	56
BILIRUBIN TOTAL	–	0.5	0.6	–	0.6
ALK PHOS	–	55	58	–	67

year-old female with schizoaffective disorder who was treated with oral risperidone. The risperidone was increased to 6 mg/day over 3 days. She developed facial and periorbital angioedema after 2 weeks of treatment. Three days after decreasing the dose to 3 mg/day, the angioedema resolved. However, when the oral risperidone was increased to 6 mg/day again, the angioedema again returned [2].

In a second case reported in 1998, a 40-year-old woman with severe refractory schizoaffective disorder was started on oral risperidone 10 mg/day over 2 months. Prior to this new medication, she had been taking valproate 90–110 μg/mL, high doses of fluphenazine for over 3 years, and clonazepam for the prior 6 months. By the end of the 2-month period, she had developed marked edema in the lower extremities and moderate edema in upper extremities. She was given diuretics, which only partially resolved her edema. However, within 1 week of decreasing the dose of risperidone to 2 mg/day, the edema resolved entirely. However, she was restarted on risperidone 8 mg/day as her psychiatric condition deteriorated, but her edema recurred [3].

The most recent case was reported in 2010, in which a 15-year-old male who was diagnosed with schizophrenia and treated with oral risperidone 1 mg/day and clonazepam 0.5 mg/day. Over a 2-week period, his symptoms had improved by 25%, at which point the clonazepam was discontinued and risperidone was doubled to 2 mg/day. Within a week of this change, he developed periorbital edema and swollen lips. Upon discontinuing the risperidone after these findings, the angioedema resolved within 1 week [4].

It is apparent that there was no specific time frame for the onset of angioedema; angioedema can occur from as little as a week to years after the initiation of risperidone. In our case, angioedema developed in the shortest amount of time, less than 24 h, compared to all other reported cases. This rapid onset of symptoms is important to note, to ensure prompt treatment and intervention in future cases.

Moreover, a commonly drawn conclusion after literature review is that risperidone-associated angioedema occurs in a dose-dependent fashion [8]. In most reported cases, the adverse effect occurs increasing the dose of risperidone, and resolves with decreasing or discontinuing the medication. There was no specific dose, however, that triggers the onset of angioedema. The doses with the reported adverse effect started from as low as 1 mg/day to as high as 10 mg/day [9]. Furthermore, Katz et al. reported a dose-dependent increase in peripheral angioedema in a large group of elderly patients [8]. In patients who received 0.5 mg/day of risperidone, peripheral angioedema occurred at a rate of 16.1% whereas an increase to 2 mg/day increased the rate to 18.1%. Our case, however, demonstrates that angioedema can develop from a one-time dose as well.

Last, another finding that is unique to our case is the simultaneous occurrence of extrapyramidal symptoms and angioedema. In 2002, Tamam et al. reported a similar case with a 27-year-old woman who experienced mild dystonia and akathisia as a result of her risperidone [10]. She had been taking oral risperidone 2 mg/day off and on for 2 years and was hospitalized for persecutory delusions and auditory hallucinations. In the hospital, she was restarted on risperidone and the dose was titrated upwards from 1 to 4 mg/day over 1 week. She began to experience some mild dystonia and restlessness during the first three weeks, which resolved with diphenhydramine administration as needed. During week 3, the patient developed moderate periorbital and facial edema along with 2+ pitting edema in both her legs. The risperidone was then decreased to 3 mg/day and the edema resolved. In this particular case, the resolution of the extrapyramidal symptoms was followed by the onset of angioedema. The patient experienced extrapyramidal symptoms while taking 2 mg/day but never had angioedema on that dose. This case further supports the dose dependent nature of risperidone's side effects, and the notion that angioedema can occur after the development of extrapyramidal symptoms. In our case, however, the patient developed increasing limb stiffness simultaneously with perioral and periorbital edema. Patients should be made aware of this combination of adverse effects and to contact their physician immediately should symptoms start to develop.

The mechanism of risperidone-associated angioedema is still unknown but there are a few hypothesized theories. Risperidone blockade of 5HT2 receptors can potentially increase cyclic adenosine monophosphate, which relaxes vascular smooth muscle and lead to edema [11]. High plasma concentrations of cyclic AMP have been noted in patients with idiopathic edema [11]. Second, it is possible that risperidone's action on muscarinic M1, histamine H1, serotonin HT2 receptors can downregulate the adenosine triphosphate-dependent calcium pump and lead to a secondary reduction in smooth muscle contractility, resulting in vasodilation and edema [11]. Finally, an immunological mechanism was suggested in the first reported case of risperidone related angioedema by Cooney and Nagy [2]. The authors hypothesized that risperidone may have further suppressed the patient's already low C1 inhibitor activity, allowing the C4-C2 activation, thereby resulting in angioedema. Terao et al. reported a patient that developed allergic reactions, including facial and pedal edema, urticaria, and disseminated maculopapular drug eruption, to risperidone when treated for epileptic psychosis. Type I and type IV allergic reactions were suspected in that patient, as IgE levels were found to be elevated [12].

The C3, C4, and C1 esterase levels were all within normal limits. Unfortunately, we did not check the IgE to assess whether this could have been attributing to the angioedema.

The etiology of the angioedema in our patient may be associated with the elevation in C3 & C4 in our patient. However, we did not check the IgE levels to indicate if that also played a role.

Furthermore, the pathophysiology behind drug induced acute dystonia also remains unclear [13,14]. It has been suggested that there may be a correlation between D2 receptors and the occurrence of dystonia. Since all antipsychotics bind to these receptors, it has been hypothesized that binding of these receptors in the globus pallidus, caudate nucleus, and putamen may result in acute dystonia [14].

Since a concrete etiology of risperidone-induced angioedema and dystonia remains uncertain, further research and clinical studies are imperative to elucidate why they occur individually as well as concurrently. This case highlights a novel simultaneous occurrence of two potentially ominous clinical entities (dystonia and angioedema), the prompt recognition of which can preclude significant morbidity in future patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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