Rapid Onset of Pedal Edema Associated with Risperidone in Two Male Patients: Simultaneous Clinical Cases

Mehmet Hamdi Orum1, Behice Han Almis2, Halis Tolga Karaca1

1Adiyaman University, School of Medicine, Department of Psychiatry, Adiyaman - Turkey
2Adiyaman University Training and Research Hospital, Department of Psychiatry, Adiyaman - Turkey

Corresponding Author:
Mehmet Hamdi Orum, MD
Adiyaman University, School of Medicine, Department of Psychiatry, Adiyaman, Turkey
E-mail address: mhorum@hotmail.com
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ABSTRACT:
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Pedal edema due to drugs is common especially with beta blockers, calcium channel blockers, non-steroidal anti-inflammatory drugs, and several hormonal drugs but they can rarely occur with new generation atypical antipsychotics. There are case reports with risperidone especially as peripheral edema. We present two male patients (Case A: 51-year-old, diagnosed with bipolar disorder type 2; Case B: 55-year-old, diagnosed with psychotic disorder plus mild mental retardation) who developed bilateral pedal edema after treatment with risperidone. Risperidone treatment in the elderly should be carefully decided because even small doses of risperidone may increase risk of edema.

Keywords: pedal edema, risperidone, male

INTRODUCTION
Risperidone is a second generation atypical antipsychotic and it is often used for the management of the psychiatric disorders such as bipolar disorder and schizophrenia. It acts by antagonizing the serotonergic (5HT2A), dopaminergic (D2, D1, D4), muscarinic cholinergic (M1), and histaminergic (H1) receptors. The most commonly seen adverse effects recorded are sedation, weight gain and orthostatic hypotension (1). Peripheral edema due to drugs is common especially with beta blockers, calcium channel blockers, non-steroidal anti-inflammatory drugs, and several hormonal drugs but they can rarely occur with new generation anti-psychotics (2). Pedal edema has been infrequently described with several atypical antipsychotics such as olanzapine (2), quetiapine (3), and risperidone (4-6). There have also been case reports of angioneurotic edema due to risperidone and periorbital edema due to long-acting risperidone (7,8). PubMed search with key terms “risperidone” and “pedal edema” revealed only two case reports on risperidone-induced pedal edema (9,10). Here, we present two male patients who developed bilateral pedal edema after treatment with risperidone which resolved spontaneously after stopping risperidone.

CASE PRESENTATIONS
Case A
A 51-year-old male patient who was being treated for bipolar disorder type 2, currently with a manic episode. He was diagnosed 25 years ago and was on maintenance treatment with sodium valproate but had poor compliance...
to medication. Previously used drugs were olanzapine, quetiapine, paliperidone, and sodium valproate. He was placed on sodium valproate 500 mg twice a day and risperidone 2 mg daily at our inpatient unit. Three days after admission, the dose of risperidone was increased to 6 mg daily because of agitation and grandiose delusion. About five days into admission, we noticed swelling of both feet and lower of legs, moderate edema up to the knee (Figure 1). There was no history of use of alcohol, cigarette and cannabis before presentation. The patient did not report any changes in his dietary and fluid intake. He was not on any drugs known to cause edema such as nonsteroidal anti-inflammatory drugs, steroids, antihypertensive, or immunosuppressive agents. The patient had diabetes mellitus but plasma glucose and HbA1c was under control. There was not a hypertensive condition. On examination, he had bilateral pedal edema. Blood pressure, cardiac, and abdominal examinations were normal. The urea, creatinine, electrolytes, thyroid function test, liver function tests, and serum proteins were normal. Urine test, chest X-ray, electrocardiogram, and Doppler ultrasonography for lower extremity were also normal. With these results, risperidone was stopped, based on emerging evidence of rare association of risperidone with peripheral edema (6,7). One week after discontinuation of risperidone, swelling completely resolved (Figure 2). He was then placed on aripiprazole 15 mg daily. This patient had used sodium valproate without a report of edema in the past.

Case B

A 55-year-old male patient was admitted to the psychiatric inpatient unit with complaints of physical aggression and decreased need for sleep, synchronously with above mentioned patient, Case A. A diagnosis of psychotic disorder plus mild mental retardation was made. The patient had no previous psychiatric admission and medications despite the older age, interestingly. He was treated by risperidone 3 mg daily and quetiapine 100 mg daily. The patient developed swelling of both feet, one week after introduction of risperidone and quetiapine (Figure 3). Physical examination of other systems were unremarkable. The urea and electrolyte, creatinine, urinalysis, liver function test, fasting blood glucose, and lipid profile were normal. Chest X-ray, electrocardiogram, and Doppler ultrasonography for lower extremity were also normal. The thyroid function test was normal. There was
no diurnal variation of edema or itching. It is decided to stop firstly risperidone and start haloperidol 5 mg daily. Within 1 week of reducing risperidone, the edema resolved (Figure 4).

Written informed consent was obtained from the patients and the relative of patients for publication of this case report and any accompanying images.

DISCUSSION

The time to onset of edema after introduction of atypical antipsychotic varies widely, from a day to several months (11,12). Peripheral edema has been infrequently described with several atypical antipsychotics such as olanzapine (2), quetiapine (3), and risperidone (4-6). In the simultaneous cases of similar ages discussed above, the pedal edema can be attributed to risperidone therapy, since edema was resolved after risperidone discontinuation. According to Naranjo’s adverse drug reaction probability scale, risperidone as a causative agent for edema can be considered probable (Naranjo’s algorithm, score 7 for both Case A and B). There have been case reports in the literature described peripheral edema associated with risperidone (4-6,13,14). There have also been case reports of angioneurotic edema due to risperidone and periorbital edema due to long-acting risperidone (7,8).

In the literature, there have been case reports about edema due to quetiapine (3). In our case B, we thought that the edema was associated with risperidone because edema was regressed after stopping risperidone and did not recur although continued to taking quetiapine. And the same mentality is valid to case A. There have been case reports about edema due to sodium valproate (15,16). In our case A, the patient has been taking sodium valproate for ten years. Pedal edema developed after adding risperidone to treatment. We thought that the edema was associated with risperidone because edema was regressed after stopping risperidone and did not recur although continued to taking sodium valproate.

Literature indicated that, in most cases, no abnormal findings were obtained in both the hematological or immunological examinations, and the exact mechanism by which risperidone caused the edema was not clear.

There are several explanations that may account for the onset of edema secondary to risperidone therapy (13,17). According to supersensitivity and vasodilatation theory, there is a super sensitivity of $\alpha$-receptors to antipsychotic which occurred during the drug-free period. The $\alpha$-receptors of the peripheral vascular system cause vasodilatation and thereby raising the hydrostatic pressure by decreasing the vascular resistance in the blood capillaries. This hydrostatic pressure moves the fluid from the intravascular compartment to the interstitial space, which leads to edema (6). Another explanation is related to dopamine receptors. Edema may be the result of antipsychotic antagonism on the renal dopamine receptors ($D_4$) thereby altering the renal regulation of fluid and electrolyte (18). According to some authors, rapid dose increase of antipsychotics may also be a factor in inducing peripheral edema. Immune components that were reported in case reports include low C₄ and C₁ esterase inhibitor in relation to risperidone (19). And also, older age has been suggested as a risk factor, especially in those with severe edema (17).

Several factors determine antipsychotic dose escalation such as history of side effects, the severity of symptoms (e.g., agitation, delusion, and hallucination), age, presence of physical health condition (20). There have been no consensus regarding to rapid dose escalation. Langan et al. (21) calculated the cumulative antipsychotic dose for an individual for days 1–15 and days 16–30 and had a ratio of first 15 days to second 15 days. The authors defined that dose escalation as a ratio of 4 times of the cumulative dose at the second 15 days compared to the first 15 days (17). But in our cases, pedal edema occurred in the first week of treatment, in discordance with literature.

Pedal edema may occur due to risperidone, if it is...
considered that risperidone is an antipsychotic drug widely used. Adverse effects like these can have negative implications on compliance to medication, especially in psychotic disorders. We hope this case sensitizes the psychiatrists/clinicians to make edema examination during risperidone treatment.

References:


