Pedal edema associated with atypical antipsychotics

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ABSTRACT

This study describes a patient diagnosed as a case of bipolar affective disorder complaining of bothersome incidence of pedal edema 1 month after the initiation of atypical antipsychotic regimen with risperidone and quetiapine. All hematological and biochemical profiles were found to be normal. On discontinuation of risperidone, the condition remained unresolved even after 2 weeks, and the edema progressed reaching her calves. On tapering the dose of quetiapine, she started showing gradual improvement in edematous condition. Quetiapine was slowly discontinued. No further recurrence of edema occurred, and hence, no further medication changes were implemented. Pedal edema was found to be resolved within weeks of dechallenge of the regimen. Naranjo adverse drug reaction probability scale gave a score of 7 which denotes “probable” adverse drug reaction with quetiapine.

KEY WORDS: Atypical antipsychotics, pedal edema, quetiapine, risperidone

Introduction

Since the introduction of the second generation or atypical antipsychotics (AAP), these agents have been widely prescribed for the management of patients with schizophrenia, bipolar disorders, other psychotic disorders, or conditions with severe behavioral disturbance. The increasing use of AAP is in part due to their lower propensity to induce extrapyramidal symptoms and tardive dyskinesia compared to typical antipsychotics.[1]

Now, more than 15 years, after the first AAP was marketed, it is observed that while extrapyramidal symptoms and tardive dyskinesia occur less frequently with atypical agents, these medications may present a different set of adverse effects. The available evidence for the association of specific antipsychotics with particular side effects, however, varies considerably ranging from weight gain, neuroleptic malignant syndrome, diabetes mellitus, hyperlipidemia, QTC interval prolongation, myocarditis, sexual side effects, and extrapyramidal side effects to cataract in patients under AAP therapy.

We report a rare case of pedal edema induced by combination therapy of two AAP, namely risperidone and quetiapine. Extensive PubMed search with key terms “risperidone” and “pedal edema” revealed only two case reports on risperidone-induced pedal edema[2,3] while search with key terms as “quetiapine” and “pedal edema” showed two reports for quetiapine-induced pedal edema[4,5] To the best of our knowledge, this is the first case of pedal edema being reported on dual therapy of risperidone and quetiapine until date.

Case Report

A 34-year-old married female reported in the outpatient unit, Department of Psychiatry, Medical College and Hospital, Kolkata, with complaints of decreased sleep, anger outburst, suspiciousness, social impairment, irritable mood increasing gradually for last 2 months. She reported of experiencing a similar episode 3 years ago. She was diagnosed as a case of bipolar affective disorder (F-31) according to International Classification of Disease: Clinical Descriptions and Diagnostic Guidelines-10. Young Mania Rating Scale (YMRS) scored 34 which further corroborated the diagnosis. She was initiated on lithium 600 mg/day and risperidone 3 mg/day. Serum lithium level was estimated on the day 5. The lithium level was found to be slightly higher than upper therapeutic range, so the physician decided to taper the dose to 300 mg/day. After 2 weeks on follow-up, the symptoms of agitation and insomnia were still

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persisting, and the quetiapine 100 mg/day and clonazepam 0.5 mg/day were added.

After 3 weeks follow-up, the patient showed significant improvement with a repeat YMRS score of 8 and risperidone dose was reduced to 1 mg daily. One month after the initiation of the therapy, the patient complained of bothersome incidence of pedal edema that, on examination, was described as bilateral 2+ pitting edema reaching up to the level of her mid calves.

She was reviewed by a physician and no physical cause for the edema was found. All hematological and biochemical profiles, including full blood count, serum albumin, lipid profile, liver function tests, thyroid function tests, urea, and electrolytes, were normal. Her blood pressure was normal; cardiac investigations such as electrocardiogram, cardiac echocardiogram troponins, and creatinine kinase were found unremarkable. Pulmonary examinations were benign. A complete metabolic profile, including albumin and thyroid-stimulating hormone, to determine etiology of her edema was found to be within normal limits. To exclude allergic etiology, immunology testing consisting of C3, C4, and IgE were normal.

Risperidone was discontinued by the psychiatrist owing to its propensity to cause pedal edema. However, the condition remained unresolved even after 2 weeks, and the edema progressed to 3+, gradually reaching her calves [Figure 1]. The dose of quetiapine was tapered to 50 mg/day. The patient started showing gradual improvement in edematous condition (Grade 2+). Quetiapine was slowly discontinued. Furosemide 20 mg/d for 10 days was prescribed symptomatically for edema, which resolved over the course of approximately 3 weeks. No further recurrence of edema occurred, and hence, no further medication changes were implemented.

Naranjo adverse drug reaction probability scale gave a score of 7 which denotes “probable” adverse drug reaction. Pedal edema was found to be resolved within weeks of dechallenge of the regimen. No rechallenge was attempted by the physician, after the withdrawal of the medication.

The temporal relationship between AAP and this incidence of pedal edema was thus established.

Figure 1: Bilateral pedal edema

Discussion

Atypical or second-generation antipsychotics such as clozapine, quetiapine, risperidone, and olanzapine are considered the first-line treatment for psychoses with many having a proven superiority over the classical mood stabilizers. In contrast to typical antipsychotics, they have minimal extrapyramidal side effects and thus tend to improve the impaired cognitive function in psychotics. AAP can potentially increase cyclic adenosine monophosphate (AMP) levels and hence relax vascular smooth muscle following blockade of 5HT2 receptors.[25] High plasma concentrations of cyclic AMP have been found in patients with idiopathic edema. It is also possible that their action on muscarinic (M1), histamine (H1), and serotonin (5HT2) receptors eventually causes downregulation of the adenosine triphosphate-dependent calcium pump which can cause a secondary reduction in smooth muscle contractility thereby resulting in vasodilatation and edema. Although there exist considerable speculations regarding potential mechanisms involved in antipsychotic-induced edema, studies have suggested an evident relationship between dopaminergic antagonism and idiopathic edema. Through a variety of receptor subtypes, dopamine may affect natriuresis, epithelial fluid resorption, vascular smooth muscle relaxation, and the renin-angiotensin system. Alternatively, alpha 1-adrenergic blocking activity of AAP has been thought to explain such cardiovascular side effects as orthostatic hypotension, dizziness, and reflex tachycardia. Alpha-adrenergic-mediated peripheral vasodilatation has also been proposed as a potential mechanism for AAP-induced edema.[30]

The temporal relationship between initiation of the medication and the appearance of edema supports the impression of an adverse reaction to AAP such as quetiapine and risperidone. Extensive cardiovascular and metabolic workups failed to reveal alternative explanations. One potential limitation of our case series is the prevalent use of medications with known associations with edema such as lithium carbonate. Although the incidence of pedal edema with AAP is believed to be not uncommon, it is not often picked up in clinical practice or reported by patients.[21] This is probably because it is usually self-limiting and transient. It will be a judicious practice to look out for this side-effect, especially during the first few days after initiating an AAP drug. It was found that pedal edema associated with AAP medications did not require much additional treatment; either reduction of the dosage or switching to a different medication is usually found to be sufficient.

Since a plausible mechanism of AAP-induced edema remains largely unknown, further clinical investigation and research are needed to elucidate the characteristics, risk factors, dose dependence, and potential mechanisms of edema associated with AAP as well as the perfect type of treatment. This case report aims to aware healthcare professionals regarding this potential vascular complication thereby promoting its prompt recognition and immediate intervention. Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.
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