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Peripheral Edema in Psychiatric Practice: A Case Series of an Unusual Adverse Effect of Risperidone Medication

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ABSTRACT

Background: *Few cases of edema associated with risperidone medication have been reported in the literature, mainly from developed countries.* ***Case report:*** *Reported here are three cases of patients who developed bilateral leg swelling each time they were commenced on risperidone. The withdrawal of risperidone in each case resulted in the resolution of the edema within few days while a re-challenge led to the re-emergence of edema.* ***Conclusion:*** *Risperidone medication is common in psychiatric practice, not only in developed but also in developing countries like Nigeria. Peripheral edema is one of its side effects, but it is rarely paid attention to by clinicians. Prescribers are reminded of this side effect and advised to regularly enquire about it and also educate their patients to report such a reaction early enough as early recognition and prompt discontinuation of the offending drug could be of great value.*

Keywords: Risperidone, Peripheral edema, Early recognition, Nigeria

INTRODUCTION

Risperidone is a novel atypical (second-generation) antipsychotic agent of the benzisoxazole derivative chemical class, widely prescribed for the treatment of behavioral conditions such as schizophrenia, schizoaffective disorder, bipolar affective disorder, and disruptive behaviors among others. It has a strong affinity to serotonin type-2 (5-hydroxytryptamine, 5-HT_{2A}), dopamine D_2, α_1- and α_2-adrenergic, and histamine H_1 receptors causing antagonism at these receptors [1,2].

The advent of the second-generation antipsychotics brought hope to mental health practitioners and their patients because of the relative reduced extrapyramidal side effects noticed with these drugs compared to their earlier counterparts - the first-generation (typical) antipsychotics. Nevertheless, these initially-much praised second-generation agents did not come without some prices too. Weight gain was one of such prices and years later, some clinicians started noticing peripheral edema among some users of the drugs [3].

Risperidone is one of the latter antipsychotics with reduced propensity to cause extrapyramidal side effects but has unfortunately been associated with peripheral edema which could be troublesome to the patient if not arrested on time [4,5]. Though few cases have been reported, many clinicians still miss the diagnosis and expose the few patients that report back to them when they develop edema (as many seek help outside mental health units) to unnecessary and expensive examinations and investigations. It becomes necessary that more of these cases are reported, especially from our country where atypical antipsychotics are being prescribed on daily basis but only one case of risperidone-related edema seems to have been reported from Nigeria [6].

Here, three cases seen over a period of six months in a treatment unit of a Nigerian federal teaching hospital are reported.

CASE REPORTS

Case 1

Mrs A is a 26-year old homemaker with a diagnosis of bipolar affective disorder, who had been managed in a hospital

in a neighboring state for over 3 years but came to our center following the family's relocation to Abakaliki. She had been on chlorpromazine, but we had to change to risperidone because she complained that in her new place of work, she needed to wake up earlier than before and chlorpromazine was making her sleep too long and wake late. We adhered to her wish but she, however, developed pedal edema after 4 days of risperidone use. The edema was bilateral, pitting, non-tender, and up to the mid-leg (Figure 1A).

Figure 1A Day 2 of risperidone medication

She was referred to the Internal Medicine unit where thorough examinations and laboratory investigations were carried out. All hematological and biochemical parameters, including Doppler ultrasound of the feet were reported to be within normal range. She was placed on anti-inflammatory drugs, but the swelling persisted. The risperidone was then withdrawn, and the edema started regressing (Figure 1B) and got completely resolved within six days. When the edema completely cleared, she objected to being snapped further by her husband (who took the pictures); claimed the husband might post the pictures in the internet and that might prevent world leaders from attending her 'forth-coming' swearing-in ceremony as the next president of Nigeria.

Figure 1B Day 3 of risperidone withdrawal

She was commenced on haloperidol and she has remained stable for many months without a re-occurrence of the edema.

Case 2

Mrs B is a 50-year old homemaker and known hypertensive that presented with a few year history of behavioral abnormalities characterized mainly by a belief that other women in the village were unhappy with her for having three prosperous male children (and for that, they were plotting against her), occasional hearing of her thoughts being spoken allowed as she was thinking them, and hearing of voices discussing her actions among themselves. She was all along being managed as a case of paranoid schizophrenia with chlorpromazine, maintained at 100 mg per night and intermittently, she received injection fluphenazine decanoate because of poor oral medication compliance. At a point she started giving one excuse or the other, alleging that the chlorpromazine was raising her blood pressure (even when the blood pressure was under control). We then placed her on risperidone, 1 mg twice daily. Two days later, she rushed to the hospital, complaining that her legs were swollen; that she was afraid because her late father who died of heart failure had similar swellings before he died. She was counseled, and the dose of risperidone reduced to 1 mg daily. But she rushed back after two days, said the edema was not resolving at all (Figure 2A).

Figure 2A Day 4 of risperidone treatment

She then requested that she be taken back to chlorpromazine which she was on for years without any body swelling. Her request was granted and within ten days, the edema, which was pitting, and non-tender gradually resolved completely (Figure 2B).

Figure 2B Day 10 of risperidone withdrawal

Mrs B had remained stable on chlorpromazine (with better compliance than before) and her usual antihypertensives for over eight months without any recurrence of edema.

Case 3

Mrs C is a 36-year married Cameroonian who has had recurrent episodes of complex partial seizure since age 25. The family had sought help only from prayer houses and traditional practitioners. She developed schizophrenia-like features and recurrent aggressive behavior 12 and 6 months, respectively, prior to presentation to us in 2017. She was

commenced on carbamazepine (controlled release, CR) 200 mg and haloperidol 5 mg, each twice daily. She came for a review a month later, reported that she never recorded any episode of seizure since her first visit but complained of rigidity and occasional up-rolling of the eyes. The haloperidol was substituted with risperidone 2 mg daily while she continued the carbamazepine. A week later, her husband called to inform that she had developed swelling of the legs which was non-pitting, non-tender and up to the knees. She presented to the hospital two days later after she had applied some local concoctions which only caused her itching and consequent skin excoriations on the legs without relieving the swelling (Figures 3A-1 and 3A-2).

Figure 3A-1 Day 9, risperidone treatment (front view)

Figure 3A-2 Day 9, risperidone treatment (side view)

The dosage of risperidone was reduced to 1 mg daily, but the edema persisted. The risperidone was then completely removed, and patient remained on carbamazepine alone. Gradually, the edema started resolving (Figure 3B) and by the seventh day, it had completely disappeared.

Figure 3B Day 3, risperidone withdrawal

Subsequently, with occasional aggressive tendencies, the haloperidol was re-introduced at a lower dose of 2.5 mg daily. She has coped very well on the carbamazepine CR 200 mg twice daily and haloperidol 2.5 mg daily. However, when her haloperidol got exhausted before her scheduled review date, she resorted to the abandoned tablets of risperidone which she took 1 mg for two nights before she noticed a re-emergence of the swelling and had to rush back to the hospital immediately. The risperidone was withdrawn and again, the edema resolved within few days.

Both the second and the third patients also received detailed evaluation by physicians and extensive metabolic work-up without any abnormality suggestive of the cause of the edema.

DISCUSSION

The three cases reported here developed marked pedal edema on initiation of risperidone. They were all females, raising the suspicion of whether the side effect is commoner in females than in males. Many case reports involved female patients [4,7] and one systematic review reported females constituting 70.6% of the sample [8].

Our third patient on her own developed pedal edema on re-challenge - an experience earlier reported [6].

Peripheral edema is more associated with drugs like anticonvulsants than antipsychotics. Though our third patient was equally on an anticonvulsant, it was clear that the anticonvulsant never caused her leg swelling but risperidone. This is similar to the cases reported where the patients on both anticonvulsants and risperidone developed peripheral edema with risperidone but never with anticonvulsants [9,10].

Calcium channel blocker is also a known agent in precipitating pedal edema. Our second patient had nifedipine in her antihypertensive regimen. She was on the drug for many years before she was commenced on antipsychotics. But she never developed any peripheral edema until she was exposed to risperidone. A similar case has been reported where the patient never developed any edema with nifedipine but did each time she took risperidone [6].

We did not bother to use a diuretic in any of the cases, because from our experience and that of other researchers [5,6], diuretics only have partial or nil effect in antipsychotic-related peripheral edema and treatment depends primarily on the discontinuation and substitution of the offending drug with another agent [5].

The exact mechanism(s) by which antipsychotics lead to edema is not very clear but various mechanisms such as the drug causing increased capillary permeability or release of proinflammatory modulators, particularly through an immunoglobulin E (IgE)-mediated mechanism (type 1 hypersensitivity reaction), and so on, have been suggested [11].

In most cases (as in the cases reported here), no abnormal finding is obtained in both the hematological or immunological examinations, and the exact mechanism by which risperidone causes the edema remains unclear [10].

In the three cases, the edema occurred within the first three days of commencing the risperidone and resolved within the first one week (10 days in the last patient) of risperidone-withdrawal which corresponds to most reports [5,6,10].

The reduction of the dosage of risperidone from 2 mg to 1 mg a day in the second and third patients did not lead to the ceasing of the edema. This goes to support an earlier report that though the edema is often dose-dependent, it could occur even with a very small dosage [5,7].

Pedal edema following atypical antipsychotics may not be as rare as is believed in some quarters. Probably because of its self-limiting nature, it is usually not reported by patients and during patient follow-up, clinicians do not enquire about that as frequently as they do for other side effects such as weight changes [12]. Our initial cases all the doctors in our department now habitually enquire about peripheral edema while reviewing patients, especially those on atypical antipsychotics [6].

An assessment of the patients presented here with the Naranjo scale - an Algorithm or Adverse Drug Reaction Probability Scale which is used to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores [13] - yielded scores of 6, 10, and 7 for the first, second, and third patients, respectively, suggesting strongly the probability of the edema being as a result of the risperidone medication.

The resolution of the edema on discontinuation of risperidone despite the retention of nifedipine (in the second case) or carbamazepine (in the third case) further buttresses that neither antihypertensives nor anticonvulsants were

contributory to the swelling, but instead that risperidone was the offending agent. The extensive physical examination and laboratory work-up by physicians never implicated any other thing or agent as the possible cause of the edema. Finally, antidiuretics and anti-inflammatory agents did not relieve the edema as long as the patients remained on risperidone.

CONCLUSION

Peripheral edema following risperidone medication might not be as rare as many think and in any case, it could lead to a serious discomfort and subsequent poor compliance on the part of the patient. Psychiatrists should take note of this side effect, enquire regularly about it from their patients, and educate their patients about it so that patients can report once they notice the side effect as early reporting followed by prompt attention of withdrawing the risperidone can save the patient, the family, and even the clinician a lot of stress.

DECLARATIONS

Consent

A written informed consent was received from each of the patients for the publication of this case series and the respective accompanying images.

Conflict of Interest

The author has disclosed no potential conflict of interest, financial or otherwise.

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