UNILATERAL FACIAL AND LIMB OEDEMA SECONDARY TO FLUOXETINE IN A PATIENT WITH HAEMORRHAGIC STROKE

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Abstract

Fluoxetine is a common selective serotonin reuptake inhibitor (SSRI) used as a pharmacological neuromodulationagent for post-stroke motor recovery and treatment for post-stroke mood disorder. Although some SSRIs are known to cause bilateral symmetrical peripheral oedema, to datethere are no reported cases of oedemacaused by fluoxetine or reported cases of a unilateral peripheral oedema. We report a case of fluoxetine-induced unilateral facial and limb oedema in a patient with haemorrhagic stroke. The peripheral oedema was noted on the hemiparetic side within 48 hours after theinitiation of fluoxetine.The medication was then tapered off over two weeks, which resulted in gradual resolution of the oedema.

Keywords: Fluoxetine, Motor recovery, Peripheral oedema, Post-stroke, SSRI

Introduction

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) anti-depressant which has an off-label use as a pharmacological neuromodulationagent for post-stroke motor recovery in both ischaemic and haemorrhagic stroke (1). Some of its most common side effects include insomnia, anxiety, agitation, and change in weight (2). Although other SSRI like escitalopram and paroxetine cause peripheral oedema as a side effect of administration (3-5) or cessation (6), fluoxetine has never been cited as a cause. We report a case of fluoxetine-induced unilateral facial, upper, and lower limb peripheral oedema in a patient with left basal ganglia haemorrhagic stroke with right-sided hemiparesis. The patient was prescribed fluoxetine for post-stroke motor recovery.

Case report

A 57-year-old gentleman with underlying hypertension, dyslipidaemia, ischaemic heart disease, and major depressive disorderpresented to us with left basal ganglia bleed(Figure 1), complicated with post-stroke seizures. Initial cognitive, speech and language assessment showed non-fluent aphasia and he was able to obey 1-step commands inconsistently. Neurological examination showed right-sided upper motor neuron facial nerve palsy, right upper limb flaccid tone with Medical Research Council (MRC) scale (7)of 0/5, and right lower limb returning tone with MRCof 2/5. There was no obvious facial or limb oedema.

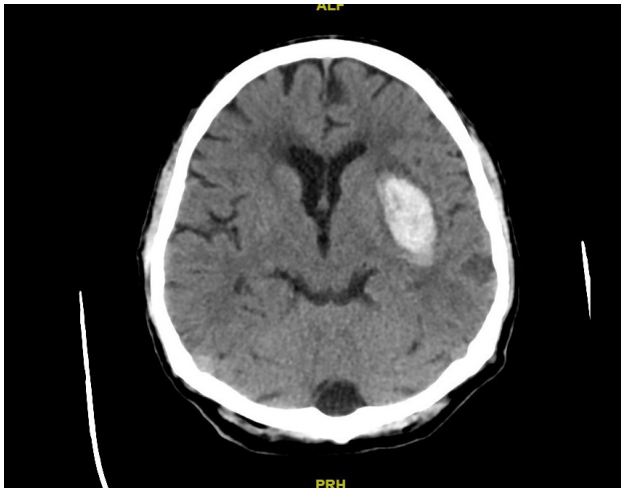

Figure 1: CT brain showing intraparenchymal bleed at the left basal ganglia measuring 4.0x2.0x2.7cm (APxWxHt) with associated perilesionaloedema and mass effect onto the frontal horn of left lateral ventricle.

He underwent intensive inpatient rehabilitation for 5 weeks, during which time he was initiated on pharmacological neuromodulation for aphasia management (piracetam 2.4g BD) and for facilitation of upper limb motor recovery. The choice of a pharmacological agent was based on earlier promising literature using fluoxetine (1, 20). He was switched from a previous prescription of sertraline 200mg OD for his treatment of depression, to fluoxetine 20mg OD to target both the depression and motor recovery simultaneously. The fluoxetine was started 1 week before his discharge from hospital, at around the 3rd week after the onset of stroke.

The patient showed cognitive, speech,and motor recovery at the end of his inpatient rehabilitation stay. He scored 21/30 (mild cognitive impairment) on Mini Mental State Examination (MMSE) (8), with deficits in attention and calculation, and recall. He had Broca's dysphasia with dysarthria, with improved intelligibility (as reported by caregiver) since the initial assessment. His right upper limb motor power had improved significantly (shoulder abduction, elbow flexion, elbow extension, wrist extension and finger extension of MRC 4/5 with a fair grip), as did his right lower limb (hip flexion, knee extension, ankle dorsiflexion and ankleplantarflexionof MRC 4/5). There was no sensory deficit. He was able to perform transfer from bed to chair independently, could ambulate with minimum assistance using a walking frame, and climbed up 2 flights of stairs using stairway guard rails for assistance. He was able to perform personal activities of daily living with moderate assistance and his overall Modified Barthel Index (MBI) (9) score on discharge was 53/100 (moderate dependency).

Upon clinic review at 2 months after being discharged, we noticed his right upper and lower limbswere swollen. The swelling was associated with dependent position regardless of level of activity. At this time, the patient has regained functional use of his right upper and lower limbs, was independent in all activities of daily living, and walked independently unaided. He denied any overt symptoms of heart failure. The swelling caused a feeling of heaviness, which affected the patient's endurance and performance in the outpatient and home therapy program.

Upon further questioning, the patient's caregiver reported that the onset of swelling was about two days after the initiation of fluoxetine, during the hospital admission and a few days before discharged. However, the swelling was very mild and not prominent;therefore he did not alert the doctors or the therapists while he was in the ward. He also complained of concomitant right-sided facial swelling, which was most prominent upon waking up in the morning after lying on his right side, but has resolved at the time of clinic review.

On examination he was able to speak in full sentences. His blood pressure was 142/98mmHg and his pulse rate was80 beats/minute with good volume. Auscultation of heart sounds showed early systolic murmur at left parasternal edge and no palpable thrill. The patient was able to obey 3-step commands consistently and had residual dysarthria but no language deficit. Neurological findings were the same as on discharge – motor power of both right upper and lower limbs were generally of MRC 4/5.

There was pitting oedemaobserved on hisright hand until the wrist joint (Figure 2a), and his right lower limb from the toes until the knee joint(Figure 2b). There was no increased warmth or tenderness over the affected limbs. The passive and active range of motion of the wrist, fingers, knee and ankle was normal and there were no other neurological deficits. There were no palpable lymph nodes. There was no facial swelling at the time of examination.

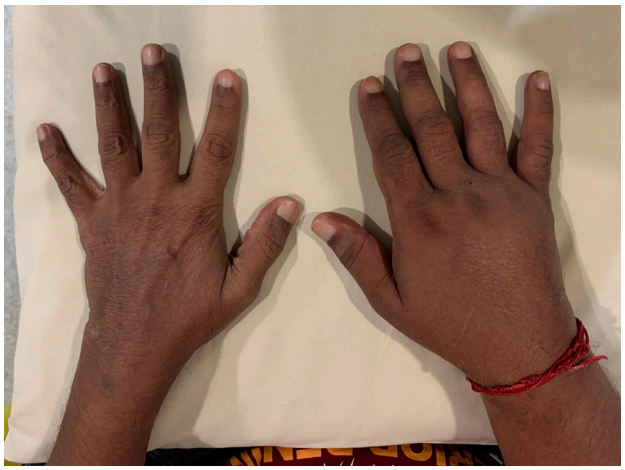

Figure 2a: Oedema of right hand

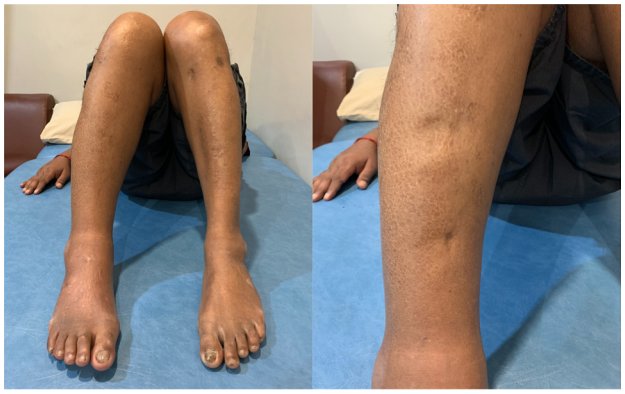

Figure 2b: Oedema of right leg over the pre-tibial area

Blood investigations showed mild normochromic normocytic anaemia (haemoglobin 12.6g/dL) and stage 2 chronic kidney disease (CKD)(10)(eGFR 64ml/min/1.73m^2) and no electrolyte imbalances (sodium 139mmol/L, potassium 3.7mmol/L, calcium 2.49mmol/L, phosphate 1.7mmol/L, magnesium 0.8mmol/L). Although the patient previously was found to have significant albuminuria (protein 3+), latest serum albumin (35g/dL) was normal. His thyroid function was also normal. Plain chest radiograph did not show any cardiomegaly, no widened mediastinum or other radiological findings suggestive of heart failure. The

patient's latest electrocardiogram was essentially normal. A prior echocardiogram, done during an admission for non-ST elevation myocardial infarction (NSTEMI) 6 months before his stroke, showed hypokinesia of the left ventricular wall and ejection fraction of 50%. Another echocardiogram was scheduled as an outpatient procedure, but was postponed because of disruptions to diagnostics services due to the COVID-19 pandemic.

A decision was made to taper down the fluoxetine from 20mg OD to 20mg every other day (EOD) for 2 weeksbefore stopping the medication completely. He was planned for outpatient review to assess his progress after cessation of fluoxetine; however in-person review was not possible because outpatient services were halteddue to the COVID-19 pandemic. His progress was assessed over the phone and the patient claimed that swelling over the face and right-sided upper and lower limbs subsided 1 month after fluoxetine was stopped.The patient denied any further improvement in his motor power or functional status.

The patient came for outpatient follow up 4 months after cessation of fluoxetine and assessment at the time showed resolution ofoedema over his face, right upper and lower limbs (Figure 3). His neurological findings and functional status remained the same as his previous assessment.

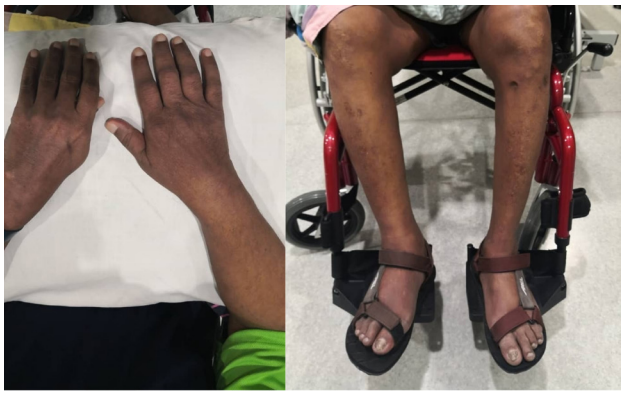

Figure 3: Resolution of oedema over theright hand and right leg

Discussion

Peripheral oedema of the hemiparetic limb after stroke is not uncommon, although its incidence varies (11). The degree of swelling correlated with hand function, whereby worse impairment and disability were reported in patients with a higher degree of swelling.Swelling of the limb can also occur despite good motor recovery (12). About 77% of these limb oedemacan be attributed to simple post-stroke hand oedema (13) while the others are possibly due to complex regional pain syndrome (CRPS) type I.Chronic lower limb pittingoedema is most commonly due to venous insufficiency, of which "dependent oedema" is a variant seen in patients with stroke (14). However, to date, there have been no published reports of oedema involving the face and unilateral upper and lower limb simultaneously, as in this patient.

Oedema of multiple sites is considered generalized and usually occurs bilaterally and symmetrically. Common causes such as heart failure, and liver cirrhosis with hypoalbuminaemia were ruled out. Although this patient has mild CKD which can result in oedema, it is usually generalized and occurs in severe renal disease (eGFR<10-15ml/min/1.73m^2) following the failure of sodium/water homeostasis mechanisms (15).Although there are reported cases of painless CRPS which presented with unilateral upper (16) orlower limb swelling without pain (17), they were preceded by trauma and had other classical clinical features of CRPS which were absent in this case.

Fluoxetine, an SSRI, was started in this patient for post-stroke motor recovery (1, 20), with added consideration given due to his background history of major depressive disorder. Escitalopram, also an SSRI, has been reported to cause bilateral lower limb oedema (3-5) which can resolve with cessation of the drug. It is postulated in those cases that the serotonergic effect of escitalopram resulted in increased vascular permeability, which is a mechanism for generalized peripheral oedema. Meanwhile, peripheral oedema has also been noted to occur with discontinuation of paroxetine (6). From the literature, fluoxetine has been reported to cause acute urticaria and facial angioedema (18) but peripheral oedema was never reported.

This patient's uncommon presentation of oedema involving the affected side of stroke was attributed to fluoxetine based on the onset of oedema which subsequently resolved when the drug was stopped, especially in the absence of further neurological or functional recovery. It is interesting to note that he did not have similar adverse effects while being on sertraline, also an SSRI, which suggests a possible link between fluoxetine and the mechanisms of post stroke limb oedema that warrants further studies.

Conclusion

In conclusion, to the best of our knowledge, this is the first report of peripheral oedemaas a possible side effect of fluoxetine that occurs in an asymmetrical pattern involving the hemiparetic side and subsiding with the cessation of the drug.The peripheral oedematemporarily affected the patient's endurance and functional performance of the recovering limbs. In view of recent evidence suggesting thatfluoxetine does not seem to improve post-stroke functional outcome (19), we recommend caution in the future use of this agent.

Competing interests

The authors declare they have no conflict of interests.

Ethical clearance

Verbal consent was obtained from the patient for his anonymised information to be published.

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References

1. FOCUS trial collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): A pragmatic, double-blind, randomized, controlled trial. Lancet. 2019;393(10168):265-74.
2. Sohel AJ, Shutter MC, Molla M. Fluoxetine. StatPearls Publishing. 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459223/. Accessed 4 January 2021.
3. Ravi PB, Ravishankar GM, Andrade C. Bilateral peripheral edema as a rare side effect of escitalopram. Indian J Psychiatry. 2014;56(1):97.
4. Tuman TC, Tuman B. A rare side effect of escitalopram: bilateral peripheral edema. Arch Clin Psychiatry. 2018;45(2):51-2.
5. Kontoangelos K, Ecomoumou M, Papageorgiou C. Ankle edema after administration of selective serotonin reuptake inhibitors. MentIlln. 2018;10:7364.
6. Mermi O, Atmaca M. Peripheral edema related to paroxetine discontinuation: a case report. KlinPsikopharmakol B. 2015;25(3):291-4.
7. Gregson JM. Reliability of measurements of muscle tone and muscle power in stroke patients. Age Ageing 2000;29:223-8.
8. Mini Mental State Examination. Shirley Ryan Ability Lab. https://www.sralab.org/rehabilitation-measures/mini-mental-state-examination
9. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for strokerehabilitation. J ClinEpidemiol 1989;42(8):703-9.
10. Ministry of Health Malaysia. Clinical practice guidelines: Management of chronic kidney disease, 2nd editionMaHTAS. 2018. Available from: https://www.msn.org.my/msn/Doc/PublicDoc_PB/CPG_Management_of_Chronic_Kidney_Disease_(Second_Edition).pdf
11. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Incidence of upper limb oedema in patients with acute hemiparetic stroke. DisabilRehabil. 2011;33(19-20):1791-6.
12. Boomkamp-Koppen HGM, Visser-Meily JM, Post MW, Prevo AJ.Poststroke hand swelling and oedema: prevalence and relationship with impairment and disability. ClinRehabil. 2005;19(5):552-9.
13. Leibovitz A,Baumoehl Y, Roginsky Y, Glick Z, Habot B, Segal R.Edema of the paretic hand in elderly post-stroke nursing patients. Arch GerontolGeriat. 2007;44(1):37-42.
14. Ely JW, Osheroff JA, Chambliss ML, Ebell MH.Approach to leg edema of unclear etiology. J Am Board Fam Med. 2006;19(2):148-60.
15. Arora P. Chronic kidney disease (CKD). Medscape. 2021. Available at: https://emedicine.medscape.com/article/238798. Assessed at 21 Sep 2021.
16. Kul A, Bagcier F, Ugur M. Painless complex regional pain syndrome in an old man. Turk J Osteoporos 2016;22(1):67-8.
17. Eisenberg E, Melamed E. Can complex regional pain syndrome be painless? Pain. 2006;106(3):263-7.
18. Tuman TC, Tuman B, Polat M, Çakır U. Urticaria and angioedema associated with fluoxetine. ClinPsychopharmacolNeurosci 2017;15(4): 418-9.
19. AFFINITY trial collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): A randomised, double-blind, placebo-controlled trial. Lancet. 2020;19(8): 651-60.
20. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): A randomised placebo-controlled trial. Lancet 2011;10(2):123-130