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Case Report

Probable fluoxetine-induced hepatomegaly: a case report

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ABSTRACT

Depressive disorder is a common behavioural, psychiatric disorder. Among various antidepressants selective serotonin reuptake inhibitors (SSRIs) are preferred drugs for the treatment of depression. When second-generation antidepressants SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used to treat depression, 0.5–1% of patients develop mildly altered liver function without any symptoms. Various degrees of organ dysfunction are linked with drug-induced liver injury, which is unpredictable and might result from exposure to a drug. We reported suspected fluoxetine-induced hepatomegaly secondary to nine weeks of treatment with an SSRI fluoxetine. Upon cessation of the agent, the patient recovered symptomatically. The evidence is vital that the hepatomegaly in this patient was caused by fluoxetine.

Keywords: Depression, Hepatomegaly, Fluoxetine, SSRIs, Adverse drug reactions

INTRODUCTION

Depression is a common illness worldwide affecting more than 300 million people. The prevalence rate is almost double in women than in men. According to World Health Organization (WHO), it was the third leading cause of illness burden globally in 2008, and by 2030, it is expected to overtake all the other causes. Among various antidepressants, selective serotonin reuptake inhibitors (SSRIs) are preferred drugs for the treatment of depression. Since it was first used in clinical settings in January 1988 after receiving FDA approval in December 1987 to treat depression, fluoxetine has become a standard first-line medication.[1] Fluoxetine has FDA approval for major depressive disorder, obsessive-compulsive disorder (age seven and older), panic disorder, bulimia, binge eating disorder, premenstrual dysphoric disorder, bipolar depression (as an adjunct with olanzapine), and treatment-resistant depression when used in combination with olanzapine.[2] Antidepressants have been linked to drug-induced liver damage, according to recent literature.[3] Various degrees of organ dysfunction relate to drug-induced liver injury, which is unpredictable and might result from exposure to a drug.[4] Drug reactions are influenced by various variables, including age, sex, and genetic makeup of the patients.[5] Most patients with depression receive SSRIs as their first-line medication since they function well and are typically more well-tolerated than other antidepressants of the patients.[6] When second-generation antidepressants such as SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used, 0.5–1% of patients have mildly altered liver function without any symptoms.[7-11] Here we discuss suspected fluoxetine-induced hepatomegaly secondary to nine weeks of fluoxetine therapy.

CASE REPORT

A 37-year-old female, multigravida living with three school-going kids, underwent ultrasonography (USG) whole abdomen in February 2022 and was diagnosed with a case of cystitis. Sonologist by USG reported that liver size was average on February 2022. She was put on symptomatic treatment for cystitis with improvement off and on. In February 2023, she also complained of sadness, generalized weakness, body aches, decreased appetite, and decreased sleep. For these symptoms, a general physician in a small town in Punjab (IN) prescribed her a capsule of fluoxetine 20 mg at bedtime and a tablet of paracetamol 650 mg as and when required without any body tests, i.e.,

complete blood counts (CBC), renal function test (RFT), liver function test (LFT) or USG whole abdomen. On general physical examination, her blood pressure was 90/70 mmHg, and her body temperature was 98^0 F. Laboratory testing revealed general physician the following results (Table 1).

Table 1: Blood investigations (at the presentation on February 2023).

Parameters	Values
Haemoglobin (g/dl)	11.1
Random blood sugar (mg/dl)	91
Serum uric acid (mg/dl)	5.0

Ultrasonography report (on 28 February 2022)

Liver was normal size (14.8 cm), shape, position, and echogenicity. No evidence of IHBR dilation/focal lesion. The portal vein appears normal in size at the porta. Hepatic veins appear normal in calibre.

Gall bladder was distended. Gall bladder shows average wall thickness without evidence of pericholecystic collection/ calculi.

CBD appeared normal in course, contour, and calibre (5.4 mm). No evident echogenic focus is seen within the visualized CBD.

Pancreas was normal in size, shape, and echogenicity. MPD (central pancreatic duct) is not dilated. No evidence of calcification of the pancreas is present. No e/o peripancreatic collection seen.

For kidneys, right kidney-10 cm, left kidney-10.5 cm. Average in size, shape, echogenicity, and position. The pelvicalyceal system is not dilated. Corticomedullary differentiation is maintained. No evidence of any mass lesion/ calculi was seen. Visualized PUJ, ureters, and VUJ appear normal. Spleen was normal in size (9 cm) and echogenicity. No evidence of splenic infiltrates.

Urinary bladder was distended. Low-level echogenic foci are seen in the lumen of UB. Wall thickness appears normal. No e/o diverticulum, calculus, or growth is seen.

The uterus appears normal in size, shape, position, and echogenicity. Endometrial thickness measures 6 mm. No evidence of fibroid/ polyp. No free fluid in POD.

Both ovaries are normal in volume and echogenicity. No obvious adnexal mass lesion was seen—no evidence of retroperitoneal lymphadenopathy/ascites present. Visualized small and large bowel loops appear normal.

Impression

USG findings reveal cystitis**.**

She was not taking any other medications. She had no history of liver disease, jaundice, or alcohol intake.

After completing nine weeks of treatment with fluoxetine 20 mg (at bedtime), she complained of right-sided abdominal pain radiating to the back, and she reported this to a private general surgeon. The surgeon advised her to have a complete blood count (CBC), urine examination, and USG whole abdomen. In CBC, there is a fall in hemoglobin and increased serum uric acid; urine examination revealed an absence of protein and sugar (Table 2).

Table 2: Blood investigations (at week 09 of treatment with fluoxetine).

Parameters	Values
Haemoglobin (g/dl)	10.2
Total leukocyte count (TLC) (/mm^3)	10200
Neutrophils (%)	70
Lymphocytes (%)	25
Monocytes (%)	02
Eosinophils (%)	03
Red blood cell (RBC) count (mill/mm^3)	3.30
Haematocrit (%)	24.6
Mean corpuscular volume (fl)	71.3
Mean corpuscular haemoglobin (picogram)	24.8
Mean corpuscular haemoglobin concentration (g/dl)	34.8
Platelet count (lakhs/mm^3)	2.35
Mean platelet volume (fl)	8.9
Platelet distribution width (%)	15.0
Plateletcrit (PCT) (%)	0.247
Red cell distribution width- coefficient of variation (RDW-CV) (%)	16.5
RDW- standard deviation (RDW-SD) (fl)	42.1
Fasting blood sugar (FBS) (mg/dl)	93
Serum calcium (mg/dl)	9.4
Blood urea (mg/dl)	35.9
Serum creatinine (mg/dl)	0.9
Serum uric acid (mg/dl)	5.5

Ultrasonography report– at nine weeks of treatment with fluoxetine

Liver was enlarged (measuring 17.3 cm) and shows normal echotexture. No apparent focal lesion is seen. Intrahepatic biliary radicles are normal.

Portal vein, this is normal at Porta. IVC is normal.

Gall bladder shows normal physiological distention. Wall thickness is standard. No evident echogenic focus was seen. There is no pericholecystic lucency or collection. No intraluminal echogenic mass with distal acoustic shadowing was seen.

Table 3: Urine examination (at week 9 of treatment with fluoxetine).

Parameters	Values
Physical examination	
Volume (ml)	30
Appearance	Clear
Colour	Light yellow
Sp. gravity	Quantity not sufficient
Reaction	Acidic
Chemical examination	
Bile salts	Absent
Bile pigments	Absent
Urobilinogen	Nil
Protein	Nil
Sugar	Nil
Microscopic examination	
Pus cells	2-4 /high power field (HPF)
Epithelial cells	Nil /HPF
Red blood cells	Nil
Crystal	Nil
Amorphous phosphate	Nil
Amorphous orates	Nil
Cast	Nil

CBD measures normal. During the examination, no obvious calculus could be seen in the visible part of CBD.

Pancreas was average in size and echotexture. Peripancreatic fat plans are preserved. The pancreatic duct is not dilated.

Spleen measures average and shows a uniform echo pattern. No focal lesion is seen. No obvious collaterals are seen at Hilum.

Right kidney was normal in shape and echotexture. Cortical thickness is standard. The cortico-medullary distinction is preserved. Few echogenic masses with distal acoustic shadowing of combined length measuring 7.2mm in the lower calyx. The pelvicalyceal system is standard with no hydronephrosis.

Left kidney was normal in shape, outline, and echotexture. Cortical thickness is standard. The cortico-medullary distinction is preserved. No echogenic mass with distal acoustic shadowing was seen. The pelvicalyceal system is standard with no hydronephrosis.

Urinary bladder partially distended with internal echoes, cystitis.

Uterus shows heterogeneous echotexture. The endometrial lining is 5.8 mm.

Both ovaries, right ovary shows a cyst of size measuring 16×14 mm – advised follow-up. She was left ovary normal in size and appearance. No free fluid was seen in the abdomen.

Impression

Hepatomegaly, advised LFT correlation right renal calculi, quarry for cystitis-advised urine C/E for clinical correlation and advised further investigations.

The general surgeon advised her medical treatment right for renal calculi and cystitis.

In this case, hepatomegaly is strongly suspected for due to nine-week treatment with fluoxetine (20 mg at bedtime) because the patient has no history of any other illness like hepatitis or any medication history like antitubercular drugs. She was advised to stop fluoxetine (20 mg at bedtime). Also, she was advised to take the herbal medicine Liv. 52 and report after one month. She started to recover symptomatically as regard improvement in appetite and meal intake.

An adverse drug reaction probability scale (Naranjo scale) was applied to this adverse drug reaction, and the score was 07. The total of the ADR probability Naranjo scale at 07 indicates causality probable (score 5-8).[12] Also, per the WHO-UMC causality assessment system, causality is probable/likely because the rechallenge was not done in the case.[13] Consent was taken from the patient for the case report, and approval from any institute was not required because a private physician made the prescription.

The drug-related ADR was reported to the Pharmacovigilance Programme of India (PvPI) by authors using the mobile App ADR PvPI, which was acknowledged on 17 April 2023.

DISCUSSION

Adverse drug reactions are a significant factor in liver damage, which may call for removing the offending medicine, hospitalization or even liver transplantation. On a regulatory level, drug-induced liver injury (DILI) is the most frequent justification for taking medications off the market, providing warnings, and changing how they should be used.[14] Recent population-based studies, however, place the incidence somewhere between 13.9 and 19.1 instances per 100,000 individuals annually.[15,16] Based on the abnormalities of liver function tests, DILI can be further divided into acute, chronic, cholestatic, hepatic, or mixed conditions.[17] The drug may produce a reactive metabolite that causes DILI or covalently bind to tissue proteins, triggering an immunological response and resulting in DILI.[18,19]

The evidence is vital that the hepatomegaly in this patient was caused by fluoxetine. No other cause was identified from history, physical examination, or investigations, and neither had a history of alcohol or other drug use. Physical examination revealed no symptoms of chronic liver

disease. Abdominal ultrasonography revealed massive hepatomegaly at the end of nine-week treatment with fluoxetine 20 mg at bedtime.

A review of antidepressants reveals that liver tests return to normal following drug cessation and that drug-induced liver impairment is modest. Rarely incidences of severe hepatotoxicity are observed.[20] Even though SSRI adverse effects are rare, understanding them is crucial. Fluoxetine can occasionally cause serious side effects. The treating physicians should be highly suspicious of SSRIs like fluoxetine which could be the reason for aberrant liver enzyme levels.[5,21]

CONCLUSION

Fluoxetine is an antidepressant medicine on the WHO Essential drugs list 2023. In this case, prescribing fluoxetine 20 mg at bedtime to a 37-year-old female is not a rational prescription by a general physician. Because there are reports of DILI with fluoxetine, the physician might have prescribed fluoxetine after going for liver function tests and ultrasonography whole abdomen of the patient and repeating the same at regular intervals.

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