

## Levofloxacin-Induced Myoclonus and Encephalopathy

Sir,

Levofloxacin is a third-generation fluoroquinolone antibiotic having broad spectrum activity and is used for treatment of a wide range of bacterial infections.<sup>[1]</sup> Though widely prescribed, levofloxacin causing neurotoxicity is a known, but very rarely seen entity with an incidence rate of 1--2%<sup>[2]</sup> and varying symptoms like headache, dizziness, sleep disturbance, psychosis, encephalopathy, ataxia, dysarthria, chorea, oro facial dyskinesia, delirium, seizures, myoclonus, and others.<sup>[3]</sup> We report a case of levofloxacin-induced encephalopathy and myoclonus, hereby highlighting a reversible and rarely suspected scenario of levofloxacin-induced neurological disorder.

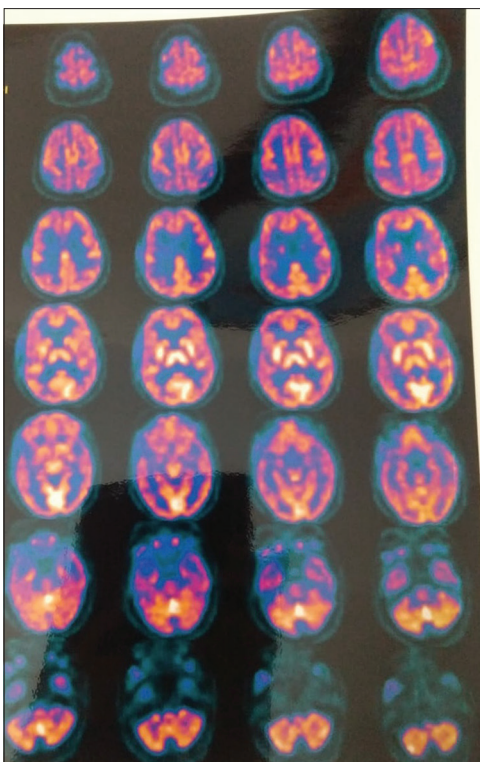
A 51-year-old male patient presented to our casualty with 3 months history of disturbed consciousness, confusion, disorientation, ataxic gait, and abnormal body movements in the form of jerks [Video 1]. Further enquiry revealed that for last 1 month patient was being administered levofloxacin (1 gm/day), ethionamide (1 gm/day), cycloserine (500 mg/day), ethambutol (1.2 g/day), pyridoxine 20 mg/day, and pantoprazole 40 mg/day for multi-drug-resistant tuberculosis (MDR-B) affecting lungs. The patient denied regular use of any other medication including traditional and herbal medications. There is no recent history of vaccination or animal bite. Patient denies any intake of alcohol.

Vitals initially recorded were as follows: blood pressure of 110/70 mm Hg, heart rate 82 beats per minute, temperature 37.8°C, respiratory rate 20 breaths per minute, oxygen saturation 98% on room air. On examination, patient was confused with a Glasgow coma scale of E3V4M5 (E-eye opening, V-best verbal response, M-best motor response). However bradykinesia, tremors, rigidity, multifocal myoclonus were present with dystonia of all four limbs. Power was 4+ in all four limbs, with brisk deep tendon reflexes and bilateral plantar flexor response. No features of malnutrition were noted. Laboratory findings revealed a white cell count of 9,200/ $\mu$ L, hemoglobin level of 12.7,

platelet count of 250,000/ $\mu$ L, ESR of 48 mm in 1<sup>st</sup> h, aspartate aminotransferase 22 U/L, alanine aminotransferase 11 U/L, alkaline phosphatase 74 U/L, blood urea nitrogen 14.5 mg/dl, creatinine 0.84 mg/dl, sodium 140 mEq/L, potassium 3.97 mEq/L, calcium 8.9 mg/dl, albumin 3.75 g/dL, thyroid stimulating hormone 5.81 IU/ml, free T3 2.97 pg/ml, free T4 0.64 ng/dl, antithyroid peroxidase antibody 1 IU/ml, ammonia 59 mol/L, vit B12 >1500 pg/ml, creatinine kinase (NAC) 90 U/L, pyruvate 0.36. MRI brain imaging was normal. Cerebrospinal fluid analysis revealed a total white cell count of 3/ $\mu$ L with lymphocytes 100%, protein 61.3 mg/dL, glucose 75 mg/dL. CSF for pan neuro viruses and autoimmune antibodies were negative. Electroencephalography (EEG) showed generalized theta slowing only. Positron emission tomography scan revealed fibroatelectatic lesion in lungs with multiple lung nodules and lymph nodes and global hypometabolism of brain with hypermetabolism in basal ganglia and thalami [Figure 1]. We could not assess antithyroglobulin antibody and serum/CSF levofloxacin levels in our patient.

The patient was empirically started on injection methyl prednisolone (1 gm daily for 5 days) along with intravenous immunoglobulins (IVIg) (30 gm daily for 5 days) initially suspecting autoimmune encephalitis (AE). With poor response at 8 days after administering methylprednisolone and IVIg, the diagnosis was still elusive. Suspecting levofloxacin as the culprit for the encephalopathy and myoclonus, it was stopped and in next few days patient started showing marked improvement. After full recovery, patient was discharged on 14<sup>th</sup> day. Patient's Naranjo adverse drug reaction probability scale registered at 6 points, which indicate a probable relationship between his symptoms and levofloxacin. Patient is well at 4 months of follow-up.

Though the literature suggests a definite association between levofloxacin and encephalopathy, we initially did not suspect it. AE was first suspected as it has a wide clinical spectrum that ranges from typical limbic encephalitis to syndromes



**Figure 1:** PET scan showing global hypometabolism of brain with hypermetabolism in bilateral basal ganglia and thalami

with neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, and coma.<sup>[4]</sup> Abnormalities noted in PET scan are highly overlapping in AE and drug-induced encephalopathy as noted in our case and cannot be solely relied upon to differentiate between the two entities.

All other potential causes of encephalopathy and movement disorders were ruled out as suggested by normal metabolic parameters and normal CSF study. After ruling out other causes, it was considered to be most likely as an adverse drug reaction to levofloxacin as few days after stopping levofloxacin, patient recovered remarkably well. With follow-up of more than 4 months, not being on any immunomodulatory therapy, temporal profile of remarkable improvement soon after stopping the levofloxacin points more in favor of diagnosis of levofloxacin-induced encephalopathy and myoclonus. Naranjo adverse reaction probability score was 6 in the present case.

Fluoroquinolone-related central nervous system (CNS) adverse reactions is a well reported but uncommon entity. One case report showed that EEG manifestation of fluoroquinolone associated neurotoxicity range from normal EEG to diffuse slowing,<sup>[5]</sup> which is present in our case. Quinolones are structurally related to GABA-A and they have a side chain at the 7 position which influences greatly in displacing GABA-A at receptor binding sites.<sup>[6]</sup> In addition to this, fluoroquinolones have been reported to affect activation of NMDA receptor.<sup>[7]</sup> The neurotoxic

potential of levofloxacin is closely related to inhibiting GABA-A receptors and activating NMDA receptors causing excessive neuronal excitatory signalling leading to neurological side effects.<sup>[8]</sup> Non-steroidal anti-inflammatory drugs, imipenem, fosfarnet, theophylline, cycloserine, fenbufen, and diphenhydramine when used along with fluoroquinolone simultaneously, it is seen that there will be increase in intensity and frequency of CNS toxicity.<sup>[9,10]</sup> Other antitubercular drugs causing encephalopathy with or without myoclonus are isoniazid, whereas ethionamide and cycloserine are not known to cause encephalopathy.

Other probabilities in our case were Creutzfeldt-jakob disease (CJD), dementia with lewy body (DLB), Hashimoto's encephalopathy (HE), and hyperammonemia which were ruled out clinically and with specific investigations. In our case, we could not find any other possible cause of myoclonus and encephalopathy other than levofloxacin neurotoxicity, and discontinuation of drug resulted in marked improvement in patient's neurological features. Levofloxacin-induced encephalopathy and myoclonus is an extremely rare but a known adverse effect and hence it should be suspected more frequently in the relevant clinical context.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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