Levetiracetam-Mediated Drug-Induced Liver Injury – A Rare Presentation and Review of Literature

Dear Editor,

Here, we report a case of thirty year old male presenting with bifrontal dull aching headache of two weeks duration that increased on coughing, sneezing and straining during defecation. This was associated with a single episode of non-projectile vomiting. The headache was relieved with symptomatic management. Magnetic resonance imaging (MRI) of the brain performed elsewhere revealed a T1 hyperintense signal with the loss of flow void on the T2 sequence in the left transverse and left sigmoid sinus, suggestive of cortical venous sinus thrombosis (CVST). The MRI also revealed T2/FLAIR hyperintense signal with mild diffusion restriction in the right thalamus, suggestive of acute infarct. Hence, he was started on Inj. low molecular weight heparin (LMWH) along with a tablet levetiracetam (LEV) 500 mg every twelve hours for seizure prophylaxis three days prior to admission. Later, he was shifted to our tertiary care hospital for further management. He had episodic mild dull aching headache on admission. A computed tomography venography of the brain was performed, which revealed thrombosis in the left superficial cerebral sinuses (transverse sinus and sigmoid sinus), deep cerebral venous sinuses (deep cerebral vein of Galen, straight sinus, and right internal cerebral vein) and the left internal jugular vein. Thus, inj. LMWH 0.6 mg subcutaneous and tablet LEV 500mg (generic) were continued every twelve hourly. The patient's liver function tests were suggestive of total bilirubin: 0.59 mg/dL (normal range: up to 1.1 mg/dL), SGOT: 23 U/L (normal range: 0–35 U/L), SGPT: 37 U/L (normal range: 0–40 U/L), LDH: 443 IU/L (normal range: 235–470 IU/L), and GGT: 15 U/L (normal range: 11–50) on admission. However, on day three of admission, the patient developed myalgia, generalized fatigability and low grade fever. On routine investigation, the patient was found to have transaminitis with SGOT –104 U/L and SGPT –152 U/L. Thus, viral markers and tropical fever workup were performed. Reverse transcription polymerase chain reaction for hepatitis A, B, C, E, and HIV returned negative. Workup for dengue, malaria, and chikungunya also yielded negative results. On day five of admission, the patient's liver function tests showed SGOT – 505 U/L & SGPT – 263 U/L with normal levels of bilirubin and GGT. The possibility of LEV-mediated

Table 1: Synopsis of 17 cases of Levetiracetam-induced drug-induced liver injury (DILI)

Study	Age (Years)/ Gender	Indication of LEV initiation	Comorbidity	Simultaneous Drugs	LEV Dosage (g/day)	Duration of LEV therapy before DILI	Histology	Proceeding	Outcome
Skopp G *et al,* 2006	22/F	H/o developmental delay and seizures	Dandy-Walker syndrome	CBZ	1 g/day	4 weeks	Hyperacute liver damage with hepatocyte necrosis	-	Death
Tan TC *et al,* 2008	21/M	Post-NCC epilepsy	-	-	N/A	4 weeks	Confluent hepatocyte necrosis	Discontinuation of LEV, Phenytoin + Dexa	LT
Lens *et al,* 2010	18/F	Epilepsy	-	Valproic acid	N/A	3 weeks	Confluent necrosis, Councilman bodies, increase of eosinophils, DRESS	Discontinuation of LEV; MPS	Improvement
Broli M *et al,* 2010	58/F	Focal seizures	-	-	1.5 g/d	4 months	-	Switch to LTG	Normalisation of LFTs
Syed A *et al,* 2012	76/M	Traumatic SDH, seizure prophylaxis with LEV	Alcohol abuse	Gabapentin, haloperidol, lorazepam, vancomycin, ceftazidime, metronidazole	1000 mg/day	4 days	-	LEV withheld	Normalisation of LFTs
Xiong N *et al,* 2012	10 month/F	Traumatic ICH, posttraumatic epilepsy	-	-	27.8 mg/kg/day	5 months	-	LEV withheld	Improvement
Gutiérrez-Grobe Y *et al,* 2013	22/F	Idiopathic seizures	Insomnia	Lacosamide 100 mg t.a.d., alprazolam 2 mg	1 g/day	8 weeks	Confluent centrilobular necrosis with reticulin collapse	Ex Lap., IPPV, ECLS	Improvement
Sethi NK *et al,* 2013	62/F	Traumatic SDH, seizure prophylaxis	N/A	Meropenem 2 g TDS	1 g/day	10 days	-	LEV withheld	Improvement
Azar NJ *et al,* 2014	25/F	New onset seizures	-	-	3 g/day	2 days	-	LEV withheld	Normalization of LFTs
Selvaraj V *et al,* 2016	50/M	Symptomatic seizures, Hashimoto's encephalopathy	HTN, COPD, methamphetamine abuse in remission	MPS, olanzapine	-	8 weeks	Moderate hepatocellular necrosis	LEV withheld and olanzapine	LT
Khoury T *et al,* 2017	N/A	LEV and temozolomide co-treatment	Cerebral neoplasm	Temozolomide	N/A	N/A	-	-	Death
Kawaguchi T *et al,* 2019	44/M	Symptomatic post-traumatic epilepsy	-	-	3 g/d	1 day	-	LEV withheld, monoammonium glycyrrhizinate, glycine L-cysteine hydrochloride hydrate	Improvement

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Study	Age (Years)/ Gender	Indication of LEV initiation	Comorbidity	Simultaneous Drugs	LEV Dosage (g/day)	Duration of LEV therapy before DILI	Histology	Proceeding	Outcome
Jayashankar S *et al,* 2019	55/M	Infratentorial ICH, seizure prophylaxis with LEV	HTN	Ceftriaxone, pantoprazole, amlodipine, Metoprolol	1 g/day	3 days	-	LEV withheld	Improvement
Gayatri P *et al,* 2020 (India)	29/M	ICH, seizure prophylaxis	HTN, alcoholism	-	N/A	5 days	-	LEV withheld	Improvement
Rogalewski A *et al,* 2021	39/F	Symptomatic epilepsy	-	-	1 g/day	2 months	Toxic pattern of damage	LEV withheld, Pred, UDCA	Improvement
Hegazy Y *et al,* 2023	76/F	Symptomatic seizure	Stroke	-	3 g/day	2 months	interface hepatitis and biliary change	LEV withheld	Improvement
Present Case (India)	30/M	Prophylaxis for seizures	CVST	LMWH	1 g/day	5 days	-	LEV withheld	Improvement

M=Male, F=Female, CBZ=Carbamazepine, NCC=Neurocysticercosis, MPS=Methylprednisolone, LTG=Lamotrigine, LFTs=Liver Function Tests, SDH=Subdural Hematoma, ICH=Intracranial Hemorrhage, HTN=Hypertension, COPD=Chronic Obstructive Pulmonary Disease, LT=Liver Transplant, Pred=Prednisolone, UDCA=Ursodeoxycholic Acid, CVST=Cerebral Venous Sinus Thrombosis, LMWH=Low-molecular-weight heparin, Ex Lap=Exploratory Laparotomy, IPPV=Invasive Positive Pressure Support Ventilation, ECLS=Extracorporeal Liver Support, Dexa- Dexamethasone

drug-induced liver injury (DILI) was considered, and LEV was withheld. After stopping LEV, liver enzymes gradually normalised (i.e from SGOT 505 U/L to 24 U/L and SGPT – 263 U/L to 59 U/L) by day fourteen of admission along with resolution of symptoms.

DILI is an adverse reaction following the administration of a drug, with an incidence ranging between 1 in 1000 and 1 in 100,000 for prescribed medication.[1] DILI is classified as either intrinsic (predictable) or idiosyncratic (unpredictable).[2] Intrinsic DILI is dose-dependent, resulting from the direct toxicity of the drug or its metabolite.[3] The most common drug causing intrinsic DILI is paracetamol. Other drugs causing this include amiodarone, valproic acid, and statins.[4] However, the majority of DILI cases are idiosyncratic or unpredictable, which is unexpected based on the pharmacological actions of the drug. Idiosyncratic DILI is further categorized as immune-mediated and genetically determined. Immune-mediated includes hypersensitivity reactions with a typically rapid onset (1–6 weeks after the initiation of medication, manifesting with fever, rashes, and eosinophilia) and drug-induced autoimmune injury (slower onset, usually without fever, rashes, or eosinophilia).[3] Minocycline and nitrofurantoin are well known to cause drug-induced autoimmune hepatitis.[4] Genetically determined DILI may also occur after months to up to one year after drug administration.[3]

The clinical manifestations of acute DILI are usually nonspecific, presenting as fatigue, decreased appetite, aversion to oily food, tender liver, and epigastric discomfort. However, the most common presentation may be asymptomatic state, with patients only showing varying elevation in the hepatic biochemical indexes, including serum SGPT, SGOT, ALP and GGT. In contrast, chronic DILI clinically manifests as chronic hepatitis, liver fibrosis, and compensated and decompensated cirrhosis.[3]

While reviewing the literature, we found that LEV-induced DILI is an extremely rare complication, with only a few reported cases. These cases, along with our case, were analyzed with respect to previous liver diseases, concomitant medications, dosage, and the duration of LEV use until DILI occurrence, along with the overall outcome. The results are summarized in Table 1.

Gayatri *et al*. have previously reported the only such case from India, that of a 29-year-old male with LEV-induced hepatic dysfunction.[5] Herein we report the second similar case from India due to its rarity. Interestingly, in contrast to their case, ours exhibited elevated transaminases alongside normal levels of bilirubin. Although the majority of cases improved with discontinuation of LEV therapy, a few resulted in mortality [Table 1].

The occurrence of DILI appears to be independent of the administered LEV dose and can occur at doses ranging from 500 mg daily up to 3000 mg daily. The duration of LEV therapy before the onset of liver dysfunction varied from one day to

five months. Histopathological analysis in patients in whom it was performed showed a range from inflammatory changes to a necrosis pattern.[6-10] Autoantibodies were reported in six cases.[5,7-9,11]

Though it is challenging to speculate about the mechanism of DILI in our case, the early onset of symptoms, along with fever, myalgia, and fatigue, suggest the possibility of immune-mediated DILI. The exact pathogenesis of idiosyncratic DILI is unknown; it is likely a complex interaction between the drug (i.e., dose, duration of the therapy, hepatic metabolism, lipophilicity) and host factors (i.e., age, sex, and genetic polymorphisms). Reactive metabolites of the drug are discussed as potential triggers for DILI or an immune response due to covalent adducts with tissue proteins.[2]

Although the patient was simultaneously on LMWH, the resolution of symptoms and normalization of aminotransferases after discontinuation of LEV temporally suggest the possibility of LEV-induced DILI. Thus, discontinuation of LEV is recommended in suspected cases. Supportive therapy with cortisone may help in severe cases. However, liver transplantation may be needed in some.[5,11]

In conclusion, although the role of primary seizure prophylaxis in CVST is unclear, as per the present consensus, prophylactic use of AEDs is not recommended. It should be considered in patients with supratentorial lesions or focal neurological deficit who present with seizures.[12] The patient was started on LEV and we continued it. The case highlights the problems caused by the unnecessary use of AEDs, and it should be avoided as far as possible. This case also serves as a strong reminder that healthcare professionals should possess a comprehensive understanding of the potential risks associated with LEV. They should also be well-versed in the effective treatment of LEV-induced DILI before deciding to prescribe it for seizure management.

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Rajendra S. Jain, Trilochan Srivastava, Pankajkumar Sharma, Ashish Pemawat

Department of Neurology, University S.M.S Medical College and Hospital, Jaipur, Rajasthan, India

Address for correspondence: Dr. Rajendra S. Jain, Department of Neurology, University S.M.S Medical College, Jaipur, Rajasthan, India.
E-mail: drrsjain@yahoo.com

References

1. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003;349:474-85.
2. Katarey D, Verma S. Drug-induced liver injury. Clin Med (Lond) 2016;16:s104-9.
3. Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM, *et al*. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int 2017;11:221-41.
4. Hosack T, Damry D, Biswas S. Drug-induced liver injury: A comprehensive review. Therap Adv Gastroenterol 2023;16:17562848231163410.
5. Gayatri P, Selvam M, Sreeharsha SV. Levetiracetam-induced hepatic dysfunction. Neurol India 2020;68:910-2.
6. Tan TCH, De Boer BW, Mitchell A, Delriviere L, Adams LA, Jeffrey GP, *et al*. Levetiracetam as a possible cause of fulminant liver failure. Neurology 200871:685-6.
7. Lens S, Crespo G, Carrión JA, Miquel R, Navasa M. Severe acute hepatitis in the dress syndrome: Report of two cases. Ann Hepatol 2010;9:198-201.
8. Broli M, Provini F, Naldi I, Bisulli F, Sama C, Baruzzi A, *et al*. Unexpected gamma glutamyltransferase rise increase during levetiracetam monotherapy. Epileptic Disord 2010;12:81-2.
9. Gutiérrez-Grobe Y, Bahena-Gonzalez JA, Herrera-Gomar M, Mendoza-Diaz P, García-López S, González-Chon O. Acute liver failure associated with levetiracetam and lacosamide combination treatment for unspecified epileptic disorder. Case Rep Emerg Med 2013;2013:634174.
10. Selvaraj V, Madabushi JS, Gunasekar P, Singh SP. Levetiracetam associated acute hepatic failure requiring liver transplantation: Case report. J Neurol 2016;263:814-5.
11. Azar NJ, Aune P. Acute pancreatitis and elevated liver transaminases after rapid titration of oral levetiracetam. J Clin Neurosci 2014;21:1053-4.
12. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F, ISCVT investigators early seizures in cerebral vein and dural sinus thrombosis: Risk factors and role of antiepileptics. Stroke 2008;39:1152-8.

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