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Case Report

Severe drug-induced liver injury caused by levetiracetam – A case report and review of the literature

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ABSTRACT

Levetiracetam (LEV) is a broad-spectrum, second-generation anti-seizure medication, which has quickly become one of the most commonly prescribed drugs for people with epielpsy due to its good tolerability, rapid up-dosing capability, with both parenteral and enteral routes of administration. Considering the frequent prescriptions and predominant excretion by the kidney with minimal hepatic metabolism, severe liver injury is very rarely a complication associated with LEV. An analysis of this reported case and further published cases was performed with respect to indication, relevant previous liver diseases, concomitant medication, and both the dosage as well as the duration of LEV when drug-induced liver injury (DILI) was noted. DILI occurs after a few days to a maximum of five months after initiation of therapy with LEV and, in the worst case, may require liver transplantation or result in death. Monitoring of serum transaminase values may be helpful. Discontinuing LEV is the first therapeutic measure. In addition, immunosuppression with cortisone can be considered for serious cases.

Introduction

Levetiracetam [(S)-α-ethyl-2-oxo-1-pyrrolidineacetamide] (LEV) is a broad-spectrum, second-generation anti-seizure medication approved for the treatment of partial seizures with and without secondary generalization. It is also approved for adjunctive treatment of myoclonic seizures, and primary generalized tonic-clonic seizures in people with idiopathic generalized epilepsy. LEV is a piracetam derivate and was approved by the United States Food and Drug Administration in 1999. In 2018, LEV was among the 100 most commonly prescribed medications in the U.S. as well as among the top seven most commonly prescribed anti-seizure medications with more than 7 million prescriptions [1]. The frequency of prescriptions has been influenced by its tolerability, rapid dosing and availability of both parenteral and enteral formulations.

In clinical trials LEV has shown an excellent tolerability profile [2]. The main dose-related adverse reactions were sedation, fatigue, and headache. Other possible adverse reactions included dizziness, unsteadiness, diplopia, nausea, infection, memory impairment, and - with relevant clinical impact - disturbances of mood and behavior. However, in controlled trials the incidences of most of these side- effects were similar compared to placebo [3].

LEV is not bound to plasma proteins and is not metabolized in the liver, so it is not expected to be associated with significant pharmacokinetic interactions [4]. The major metabolic pathway of LEV is independent of the hepatic cytochrome P450 system. There is no inhibition or induction of hepatic enzymes by LEV. Sixty-six percent of the administered dose is excreted unchanged in the urine; 24% is metabolized to an inactive metabolite that is detectable in the blood and is also excreted in the urine [5]. Elevated liver enzymes are reported in < 1% of patients following treatment with LEV [6]. Because of its low potential for drug-drug interactions, LEV is also considered beneficial in patients with seizures undergoing liver transplantation [7,8] or patients with chronic liver diseases and epilepsy [9]. Due to renal excretion, a reduction in the daily maintenance dose of LEV is recommended for patients with concomitant renal impairment. However, no dose

Abbreviations: LEV, Levetiracetam; DILI, drug-induced liver injury; InDILI, intrinsic DILI; IDILI, idiosyncratic DILI.

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adjustment is required for patients with mild to moderate liver impairment.

Drug-induced liver injury (DILI) is an adverse reaction following drug administration with an incidence between 1 in 1000 and 1 in 100,000 in patients taking medications as prescribed [10]. DILI can be classified as either predictable (intrinsic) or unpredictable (idiosyncratic) [11]. Intrinsic DILI (InDILI) is closely correlated with the drug dose and has a short latency period of a few days, which is due to direct toxicity of the drug or its metabolite [12]. An example of InDILI is acetaminophen overdose [13]. However, the majority of DILI is unpredictable or idiosyncratic (IDILI) – it is unexpected based on the pharmacological actions of the drug. IDILI can occur as immune-mediated and genetically determined. Immune-mediated IDILI include hypersensitivity with typically rapid onset (1–6 weeks after initiation of medication, manifestation with fever, rashes, increased eosinophils) and drug-induced autoimmune injury (slower onset, usually without fever, rashes, increased eosinophils, in some cases characteristic antibodies including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC)). Genetically determined IDILI may also occur after months up to one year after drug administration [12].

We herein report a case of a young woman with DILI two months after starting therapy with LEV. Furthermore, this case is contextualized within further reported cases of DILI due to LEV by means of a systematic Pubmed literature search.

Case presentation

A 39-year-old female patient was treated with LEV 500 mg twice daily due to focal epilepsy. The structural focus of the seizures was a suspected low-grade right frontal precentral glioma detected on MRI (see Fig. 1A-D). This had become conspicuous by left-sided facial hypesthesia and central facial paresis.

Recurrent focal aware seizures with motor manifestations of brief rhythmic clonic twitching of the left arm was noted one to two times daily followed a Todd's paralysis with transient left hand weakness. No focal impaired awareness seizures or focal to bilateral tonic-clonic seizures were present. An EEG was normal and following administration of LEV the patient became seizure-free.

Early risk factors for epilepsy, relevant prior medical conditions, and drug allergies were not could be uncovered as a cause for epilepsy in this patient. MRI brain facilitated a biopsy with neuropathological evaluation of a focal lesion that was suspected to be a frontal lobe glioma revealed normal central nervous system tissue with reactive gliosis, and molecular biology studies yielded no evidence of neoplasia.

After biopsy was performed, acetaminophen was prescribed on an as-needed basis due to headache, maximum 2000 mg daily for one week. In addition, therapy with metamizole was given. Three weeks after the brain biopsy, analgesic therapy was no longer required. No medication was required after this period.

Two months later, the patient was admitted to the gastroenterology service because of vomiting and jaundice that had been present for one week. A laboratory examination revealed hyperbilirubinemia (14.2 mg/dl; direct bilirubin 11.57 mg/dl), elevated transaminases (AST 975 U/l, ALT 758 U/l, GGT 308 U/l), elevated alkaline phosphatase (198 U/l) as well as LDH (410 U/l) and coagulation abnormalities (INR 1.8). Other laboratory parameters with regard to possible causes of liver injury were unremarkable including anti-HAV, anti-Hbc, anti-HCV, HCV RNA-PCR. Abdominal ultrasonography described cholecystolithiasis without any evidence of biliary dilatation or vascular abnormalities. Choledocholithiasis was excluded by endoscopic ultrasound. In order to clarify the laboratory profile with suspected toxic drug-induced liver damage, a liver biopsy was performed without complications. The histologic aspect was consistent with toxic pattern of liver injury with centroacinar-accentuated necrosis of the liver parenchyma, affecting approximately 25% of the cells. Portal fields were partially maintained, some with an inflammatory cell infiltrate. In part, the centro-acinar necroses merged into portal fields. In staining for CK7 increased cholangio-cellular reaction indicating regeneration/reparation was present. There was significant parenchymal damage with corresponding accompanying cellular reaction and mild to moderately dense inflammatory cellular infiltration in the portal fields (see Fig. 2A-C).

LEV administration was discontinued immediately after admission. Anti-seizure therapy with lacosamide 50 mg twice daily was initiated. In addition, treatment with prednisolone 1 mg per kilogram body weight daily and ursodeoxycholic acid (500 mg twice daily) was initiated. Due to coagulation impairment, vitamin K was also administered. Prednisolone was gradually reduced within the next two weeks. As a result of this apporach to therapy a complete biochemical response with restoration of liver function was achieved without any evidence of persistent liver damage during the follow-up of 9 months. The time course of the liver serum parameters obtained as laboratory tests are displayed in Fig. 3.

Methods of literature review

A systematic Pubmed search was performed in February 2021 with the search criteria "levetiracetam" and "liver" with display of 127 publications. Among these were a total of 14 case reports of acute liver failure in patients receiving therapy with LEV [6,14–26].

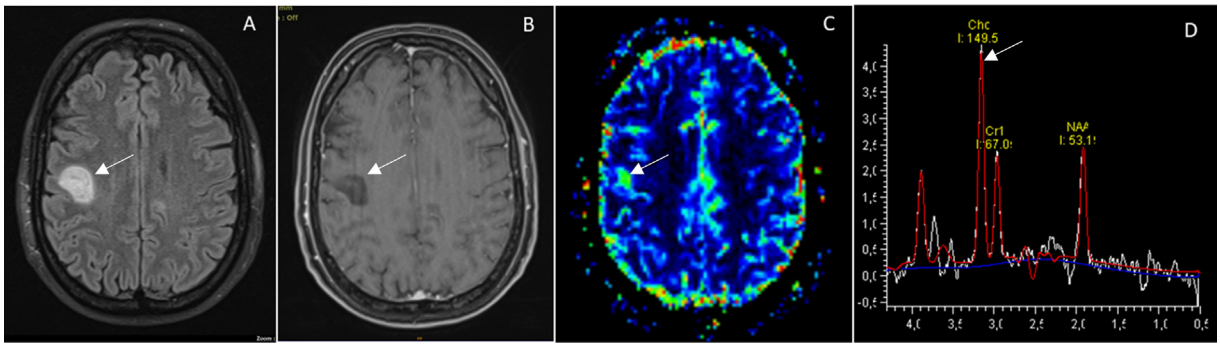

Fig. 1. A-D: MRI of a mass lesion along the right-sided precentral gyrus. (A) FLAIR measurement showing a smooth bordered, hyperintense mass in the right precentral gyrus without significant perifocal edema. This lesion shows no contrast enhancement (B), but a circumscribed increase (C, arrow) of the regional cerebral blood volume (rCBV) as well as a clear increase (D, arrow) of the choline peak on MR spectroscopy (SVS SE 135).

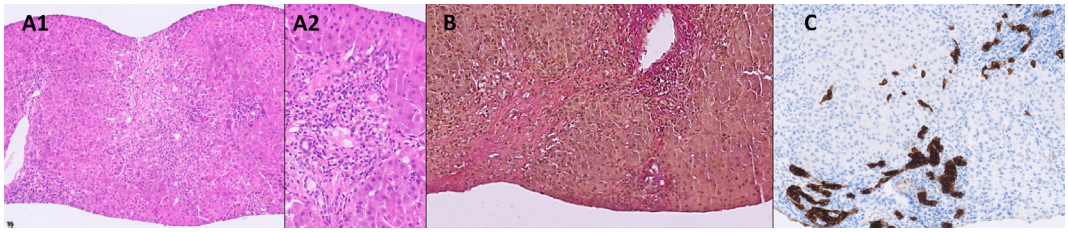

Fig. 2. A1 + A2: Inflammation and reparation in a portal tract and loss of hepatocytes around the tracts. Additionally centroacinar necrosis is seen, indicating the damage (H&E, A1: original magnification 10x20, A2: 20x magnification). B: Fibrosis and beginning cirrhosis with increased portal and perisinusoidal collagen. Some of the portal tracts start to connect with each other gibing the aspect of a regenerative nodule (EvG, original magnification 10x20). C: Immunostaining for CK7 decorates increased number of cholangiocellular reactions in the ductal plate as a sign of regeneration (CK7, original magnification 10x20).

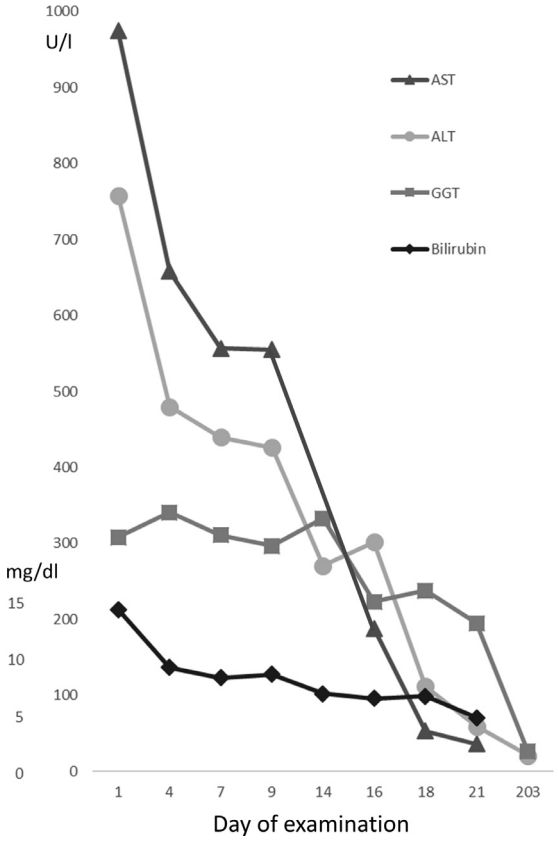

Fig. 3. Illustration of liver parameters AST (triangle), ALT (circle), GGT (square) and bilirubin (diamond) over time on days 1, 4, 7, 9, 14, 16, 18, 21 and as a late control after 203 days. Please note that AST, ALT and GGT parameters were measured in U/l, while bilirubin was measured in mg/dl.

Discussion

Considering the frequent prescription of LEV, reported DILI is a very rare complication. 14 published cases related to our case report were identified and analysed with respect to indication, relevant previous liver diseases, concomitant medication, both dosage and duration of LEV until DILI occurred as well as overall outcome. The results are presented in Table 1. None of the reported cases showed pre-existing liver disease or other possible triggering factors. In general, a history of pre-existing liver disease has been reported in about 10% of a multicenter and prospectively enrolled cohort including 660 adults with definite, highly likely, or probable DILI of different etiologies [27]. No patients with LEV therapy were reported in this cohort.

The occurrence of DILI was apparently independent of the applied LEV dose and occurred at doses of 500 mg daily up to 3000 mg daily. The duration from the start of LEV administration to the onset of liver dysfunction varied from one day to five months. The histopathological analysis is characteristic of hepatocellular damage with necrosis pattern in patients with biopsy performed. One biopsy showed an eosinophilic pattern, with a diagnosis of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome [20]. DRESS syndrome is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period. It is followed by a variety of clinical manifestations, usually fever, rash, lymphadenopathy, eosinophilia, and a wide range of mild-to-severe systemic presentations [28]. In some other cases with histological examination, an accompanying inflammatory reaction was described. Five case reports [18,20,21,24,26] mentioned the determination of autoantibodies, but in each without detection. In some cases, the specific antibodies were reported in detail, in other cases solely hepatitis antibodies were reported, and in some cases autoimmune screening was reported in summary.

Our case report occurred during monotherapy with LEV, so causality of co-medication can be excluded, which is in line with six other reports [16,18,19,21,23,26]. A precise description of possible additional influencing factors, especially other associated medications (even over-the-counter medications) cannot be traced in all reports, especially not in the ones were co-medication with temozolomide was reported [15] or with existing alcohol abuse [22]. For this reason, the consideration of cases on LEV monotherapy is of particular importance. DILI occurred within the first five days in three cases. In two of these cases, the administered dose was 3000 mg daily [16,26]; in one case, the dose was not reported [18]. The remaining cases of monotherapy reported the onset of DILI between one and five months after initiation of LEV medication, consistent with our case report.

The exact mechanism of hepatotoxicity of LEV is unknown, but is likely to be a hypersensitivity reaction. It may be discussed as an idiosyncratic DILI with a distinct spectrum of histopathological pattern (hepatocellular, cholestatic, and mixed) [11]. In addition, an immune-mediated form and a non-immune-mediated form are distinguished. In the immune-mediated form, the latency is shorter (1–6 weeks) compared with non-immune mediated reactions (1 month to 1 year). These described latencies concur well with the latencies of the published cases described here. A prospective study including 899 patients with DILI showed a higher prevalence in women (59% female versus 41% male) [29], which also corresponded to the LEV associated reports (57% female versus 43% male).

The exact pathogenesis of idiosyncratic DILI remains unknown. It is most likely a complex interaction between drug (e.g. dose, duration of therapy, hepatic metabolism, lipophilicity) and host factors (e.g., age, sex, genetic polymorphisms). In part, reactive metabolites of the drug are discussed that may trigger DILI or an immune response as a result of covalent adducts with tissue

Table 1
Synopsis of 14 published cases related to our case report with respect to patient's age and sex, indication of LEV, comorbidity, concomitant medication, both dosage and duration of LEV until DILI occurred, histology of liver biopsy (if performed), proceeding as well as overall outcome.

Study	Age / sex	Indication of LEV therapy	Comorbidity	Co-medication	LEV-dosage	Treatment duration before adverse event	Histology	Proceeding	Outcome
Skopp 2006	22 years/ Female	History of developmental delay and seizures	Dandy-Walker syndrome	Carbamazepine	1000 mg/d	4 weeks	Hyperacute liver damage with hepato-cyte necrosis	-	Death
Tan 2008	21 years/ Male	Post-neurocysticercosis epilepsy	-	-	Not reported	1 month prior switched from oxcarbazepine to LEV	Confluent hepatocyte necrosis	Discontinuation of LEV Phenytoin + Dexa-methasone	Liver transplantation
Lens 2010	18 years/ Female	Epilepsy	-	Valproic acid	Not reported	3 weeks	Confluent necrosis, Councilman bodies, increase of eosinophils, DRESS	Discontinuation of LEV Methylprednisolone with tapered dosage	Improvement normal liver tests after 9 months
Broli 2010	58 years/ Female	Partial epileptic seizures	-	-	1500 mg/d	4 months	-	switch to lamotrigine	Decrease of liver enzymes
Syed 2012	76 years / Male	Traumatic subarachnoid hemorrhage, seizure prophylaxis with LEV	Alcohol abuse	Gabapentin, haloperidol, lorazepam, vancomycin, ceftazidime, metronidazole	500 mg twice daily	4 days	-	Discontinuation of LEV	Improvement of liver function
Xiong 2012	10 months / Girl	Traumatic intracranial hemorrhage, posttraumatic epilepsy	-	-	27.8 mg/ kg/d	5 months	-	Discontinuation of LEV	Improvement
Gutiérrez-Grobe 2013	22 years / Female	Seizures of unknown etiology	Insomnia	Lacosamide 100 mg t.a.d., alprazolam 2 mg	500 mg twice daily	2 months	Confluent centrilobar necrosis with reticulin collapse	Exploratory laparotomy, invasive ventilation for 10 days, extracorporeal liver support for unique occasion	Improvement clinically and biologically
Sethi 2013	62 years / Female	Traumatic subdural hematomas, bifrontal craniotomies, seizure prophylaxis	Not reported	Meropenem 2000 mg every 8 h	500 mg twice daily	10 days	-	Discontinuation of LEV	Improvement
Azar 2014	25 years / Female	New onset convulsive episodes	-	-	3000 mg/d over 1 week	2 days	-	Discontinuation of LEV	Normalization
Selvaraj 2016	50 years / Male	Seizures secondary to Hashimoto's encephalopathy	Hypertension, COPD, tobacco abuse, methamphetamine abuse in remission	Methylprednisolone, olanzapine		8 weeks	Moderate hepatocellular disarray, hepatocellular necrosis etiology undetermined	Discontinuation of LEV and olanzapine	Liver transplantation
Khoury 2017	n.a.	Case-control study LEV and temozolomide co-treatment	Brain neoplasm	Temozolomide	n.a.	n.a.	-	-	Death
Kawaguchi 2019	44 years / Male	Symptomatic epilepsy after brain trauma	Drinking habit	-	3000 mg/d	1 day	-	Discontinuation of LEV, monoammonium glycyrrhizinate, glycine L-cysteine hydrochloride hydrate	Improvement
Jayashankar 2019	55 years / Male	Cerebellar bleeding, forth ventricle compression, seizure prophylaxis with LEV	Hypertension	Ceftriaxone 3 × 1 g, pantoprazole 2 × 40 mg, amlodipine 2 × 5 mg, Metoprolol 2 × 50 mg	500 mg twice daily	3 days	-	Discontinuation of LEV	Improvement
Gayatri 2020	29 years / Male	Intracranial hematoma, seizure prophylaxis	Hypertension, alcohol consume	-	not reported	5 days	-	Discontinuation of LEV	Improvement
Present case	39 years / Female	Structural epilepsy	-	-	500 mg twice daily	2 months	Toxic pattern of damage	Discontinuation of LEV, prednisolone, ursodeoxycholic acid	Improvement

LEV, levetiracetam; n.a., not available.

proteins [11]. In the published case reports, as mentioned above, hepatoxicity occurred in half of the cases without administration of concomitant medications, so an interaction seems very unlikely.

With regard to therapy, an improvement of liver enzymes and liver function after discontinuation of levetiracetam administration was reported, thus discontinuation of LEV is recommended in suspected cases. Supportive therapy with cortisone was given in three cases including our case report resulting in good outcome and hepatic recovery. However, four cases displayed a poor outcome: liver transplantation was required in two cases [6,19], and two patients died [14,15]. Chronic or persistent injury following recovery from levetiracetam therapy has not been reported.

The incidence of DILI secondary to LEV is very low and the prevalence can only be estimated. In general, the incidence of DILI is between 1 in 1000 and 1 in 100,000 in patients taking medications as it has been prescribed [10]. LEV is also available as a generic. Extrapolating prescriptions worldwide, reports of DILI account only in a fraction of cases that have occurred during treatment with LEV. We would estimate a range of occurrence of DILI associated with LEV resulting in improvement in liver function after discontinuation to be approximately 1 in 100,000 to 1 in 1.000,000. The incidence of a severe outcome requiring liver transplantation or resulting in death is estimated to be far below 1 in 1.000,000.

Conclusion

DILI following therapy with LEV is an extremely rare event, but in rare cases can lead to liver transplantation or even result in death. Pre-existing liver disease and possiblely other precipitating factors such as co-medication do not appear to play a major role in our case. It may therefore be considered as a case of idiosyncratic DILI, with onset noted after a few days to a few months following initiation of LEV. Clinicians using LEV should be aware that DILI may occur in association with LEV despite the lack of significant hepatic metabolism and known pharmacokinetics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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