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ASYMPTOMATIC TRANSAMINITIS IN EPILEPSY PATIENT: A HIDDEN RISK OF LONG-TERM ANTIEPILEPTIC DRUG USE

Pertiwi I Gusti Agung Ayu Ary Indah[1], Astri Asvinia Made[2], Sumada I Ketut[3], Yuliani Desie[4], Jayanthi Ni Made Kurnia Dwi[5]

[1,2]Intern of Neurology Department in Wangaya Regional General Hospital, Denpasar, Bali, Indonesia

[3,4,5]Neurologist Department of Neurology Wangaya Regional General Hospital, Denpasar, Bali, Indonesia

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Abstract: **Introduction: Long-term antiepileptic drug (AED) therapy is essential in managing chronic epilepsy, but it carries the risk of hepatotoxicity—often presenting as asymptomatic transaminitis. This case report highlights a patient with significant liver enzyme elevation without clinical signs of liver dysfunction.**

Case Illustration: Female 19-year-old with a history of epilepsy since the age of 4 years presented to the emergency department with a seizure episode. She had been on long-term polytherapy with levetiracetam (2×500 mg), divalproex sodium (3×500 mg), carbamazepine (3×500 mg), and phenytoin (3×100 mg). Laboratory tests showed elevated SGOT/SGPT levels (413/260 U/L) without any clinical manifestations of liver dysfunction. Viral hepatitis screening was negative, and the elevation was suspected to be related to cumulative hepatotoxic effects of her AED regimen. She was advised to undergo routine liver function monitoring and consider adjusting to less hepatotoxic agents.

Discussion: Asymptomatic transaminitis is a recognized but often under-monitored complication of long-term AED use, particularly in combination therapy. Treatment with lipophilic antiepileptic drugs such as valproic acid, phenytoin, and carbamazepine have high hepatotoxic potential, while newer agents like levetiracetam are more suitable for patients with liver disease. The absence of hepatoviral infection markers in this case supports the suspicion of drug-induced liver injury.

Conclusion: Asymptomatic transaminitis may occur as complication of long-term AED use, particularly in combination regimens. Routine monitoring of liver function is essential in epilepsy patients undergoing chronic therapy to facilitate early detection of hepatotoxicity and prevent serious complications.

Keywords: **Antiepileptic drugs, Epilepsy, Hepatotoxicity, Long-term use, Transaminitis.**

I. INTRODUCTION

The long-term use of antiepileptic drugs (AEDs) has become an essential component in the management of epilepsy, where appropriate therapy aims to prevent seizure recurrence and improve patients' quality of life. However, chronic use of AEDs can induce several adverse effects, most notably asymptomatic transaminitis. Transaminitis refers to an elevation in liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which often goes unnoticed yet poses a significant hidden risk.[1]

The mechanism of AEDs can influence hepatic metabolism, leading to enzyme imbalances that result in increased transaminase levels. Certain AEDs—such as valproic acid, carbamazepine, phenytoin, and phenobarbital—are known to affect liver function, with nearly 50% of patients showing elevated ALT and AST levels.[2] Genetic predisposition and underlying health conditions may also contribute to an individual's susceptibility to AED-induced side effects, highlighting the importance of liver function monitoring among patients undergoing long-term therapy.[3]

Routine liver function monitoring is strongly recommended to detect potential asymptomatic transaminitis resulting from AED use. According to the American Association for the Study of Liver Diseases (AASLD), early detection and appropriate management of drug-induced transaminitis are crucial to preventing more severe hepatic injury.[4]

This case report, therefore, presents a patient with epilepsy who had been on long-term multi-AED therapy and was found to have elevated transaminase levels without any clinical signs of liver dysfunction.

II. CASE REPORT

A 19-year-old female patient presented to the Emergency Department with a complaint of a single episode of seizure prior to hospital admission. The seizure was characterized by upward eye deviation and tonic rigidity of the arms and legs. The episode lasted less than two minutes, followed by postictal fatigue and sleep. The patient also reported experiencing three seizure episodes two days before admission, each followed by confusion and weakness. Additionally, she had complaints of fever and nausea starting one day prior to arrival.

The patient had a history of febrile seizures at 11 months of age, initially presenting with a three-day fever and diagnosed with dengue hemorrhagic fever (DHF) upon hospital admission. The first seizure occurred on the first day of hospitalization, following a blood test. The episode lasted approximately two minutes and was followed by sleep and fatigue.

At the age of four, the patient began experiencing recurrent seizures. The seizures typically began with a smile, followed by upward eye deviation and circular limb movements, lasting around one minute. Prior to these seizures, she often refused to eat, and postictally she regained consciousness and spoke normally. According to her mother, seizure frequency progressively increased, with episodes occurring three to four times a day over the past week. Her parents also reported a peculiar sensation of impending urination before each seizure episode.

She was initially treated with valproic acid syrup at 2.5 ml twice daily until the age of five. A missed dose by two hours once led to a seizure recurrence. At age ten, her therapy was escalated to two antiepileptic drugs (AEDs) valproic acid and carbamazepine. Despite treatment, she continued to experience monthly seizures through junior high school. The regimen was later expanded to three AEDs—valproic acid, carbamazepine, and phenytoin. At age 18, levetiracetam was added, making it a four-drug regimen. She has been seizure-free for the past year on this combination.

Her current antiepileptic regimen includes levetiracetam 500 mg twice daily, divalproex sodium 500 mg three times daily, carbamazepine 500 mg three times daily, and phenytoin 100 mg three times daily.

The patient's father had a history of seizures in childhood but was never diagnosed with epilepsy. There was no reported family history of other chronic illnesses. The patient was enrolled in a vocational high school but eventually dropped out due to difficulties keeping up with her studies.

Physical Examination the patient was alert and oriented (GCS E4V5M6). Her vital signs were as follows: blood pressure 111/51 mmHg, heart rate 90 bpm, respiratory rate 20 breaths per minute, and body temperature 36.7°C. General physical examination was within normal limits. No scleral icterus was observed, and she denied right upper quadrant abdominal pain. Neurological examination revealed no focal deficits.

Laboratory examinations that have been carried out are AST, ALT, HBsAg and anti-HCV.

TABLE I: LIVER ENZYMES

Test	Result	Unit
ALT	260	mg/dl
AST	413	mg/dl

TABLE II: OTHERS

Test	Result	Unit
HBsAg	Negative	Negative
HCV	Negative	Negative

The patient was diagnosed with epilepsy and drug-induced transaminitis. She was managed with intravenous fluids (0.9% NaCl at 20 drops/min) and continuation of her current antiepileptic regimen: levetiracetam 2 × 500 mg PO, divalproex sodium 3 × 500 mg PO, phenytoin 3 × 100 mg PO, carbamazepine 3 × 500 mg PO, with diazepam PRN for seizures.

Internal medicine consultation recommended supportive hepatic therapy, including omeprazole 40 mg IV twice daily, curcumin supplement twice daily, and sucralfate 15 mL three times daily. The team advised consideration of switching to less hepatotoxic AEDs and scheduled follow-up for ALT/AST monitoring and abdominal ultrasound via outpatient clinic.

III. DISCUSSION

Epilepsy is a neurological disorder characterized by recurrent epileptic seizures caused by paroxysmal, excessive, and abnormal electrical discharges from cortical neurons, and is attributable to various etiologies rather than acute brain disease.[5] According to the International League Against Epilepsy (ILAE), the causes of epilepsy are classified into six categories: genetic, structural, infectious, metabolic, immune, and unknown origins.[6] Seizures occur due to a sudden imbalance between excitatory and inhibitory forces within cortical neuronal networks. This imbalance typically arises from reduced inhibitory transmission—such as after administration of GABA antagonists or withdrawal of GABA agonists—or enhanced excitatory activity, including increased action of neurotransmitters like glutamate or aspartate.[7] Epileptic seizures may be triggered in predisposed individuals by several factors. Common provokers include hyperventilation and photostimulation (e.g., flashing lights or rapidly changing visual patterns). Additionally, physical or emotional stress, sleep deprivation, sensory overstimulation, and hormonal fluctuations related to menstruation, puberty, or pregnancy have been associated with increased seizure frequency.[6]

Transaminitis refers to an elevation of liver enzymes, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicating potential liver injury. The use of antiepileptic drugs (AEDs) such as valproic acid, carbamazepine, and phenytoin has been documented to cause transaminitis as a side effect. [8] The primary goal of epilepsy treatment is to reduce seizure frequency and enhance patients' quality of life, with careful monitoring for adverse drug effects.

The mechanism by which valproic acid induces transaminitis is related to its hepatic metabolism, primarily through glucuronidation and oxidation. These pathways produce metabolites that may be hepatotoxic. [8] One such metabolite is ammonia, which may impair hepatocyte function, induce oxidative stress, and contribute to hepatic inflammation. Studies have shown that the resultant liver damage is more likely due to the accumulation of these toxic metabolites rather than direct cellular injury. [8][9] Research has shown that valproic acid significantly increases ALT levels by up to 9.1%. In some cases, although liver enzyme levels may be elevated, patients may not exhibit clinical symptoms, thus being referred to as asymptomatic.[7]

Individual susceptibility—such as genetic predisposition, treatment duration, and drug interactions—also plays a significant role in the risk of developing transaminitis. Long-term use of valproic acid increases the likelihood of hepatotoxicity. Hence, routine monitoring of liver function is recommended, particularly for patients receiving high doses.[10]

Carbamazepine is a potent inducer of cytochrome P450 enzymes, especially CYP3A4, which is critical in drug metabolism and hepatic processing.[11] Its enzymatic induction increases reactive metabolite production and oxidative stress in hepatocytes, potentially leading to asymptomatic transaminase elevation. A study by Devarbhavi et al. indicated that long-term carbamazepine use is associated with increased liver enzymes and a heightened risk of hepatic complications.[12]

Phenytoin is metabolized in the liver by CYP2C9 and CYP2C19, following a mechanism akin to carbamazepine.[13] In some cases, phenytoin may trigger immune-mediated hepatotoxicity, potentially through hapten-protein interactions, eliciting autoimmune-like hepatocellular injury.[7] Although rare, this immunologic response can lead to hepatic inflammation and elevated transaminase levels.

In contrast, levetiracetam, a newer broad-spectrum AED, is considered liver-friendly. Approximately 66% of the drug is excreted renally, 24% undergoes enzymatic hydrolysis, and less than 2% is metabolized by hepatic enzymes, making the risk of hepatotoxicity low.[14] No dosage adjustment is typically necessary in patients with mild to moderate liver impairment, although in those with severe liver disease (e.g., Child-Pugh Class C), dose reduction is advised to minimize toxicity. [14]

A previous study conducted on children in India showed that the use of carbamazepine, valproic acid, and phenytoin could lead to increased AST and ALT levels after one year of use. Although other changes in AST and ALT levels were not significant with monotherapy, monitoring at 6 and 12 months is recommended for treatment durations of one year or more.[15] If AST/ALT elevations are less than 3 times the upper limit of normal and the patient is asymptomatic, closer monitoring is advised, typically with repeat testing in 2–4 weeks. However, if AST/ALT levels rise to more than 3 times

the upper limit of normal or the patient shows clinical signs such as jaundice, abdominal pain, fever, nausea, vomiting, or malaise, a more thorough evaluation should be conducted, with repeat testing in 1–2 weeks, while considering discontinuation or substitution of the drug.[16]

Lipophilic AEDs require hepatic metabolism to convert into hydrophilic forms suitable for renal excretion. This biotransformation involves Phase I reactions (oxidation, reduction, hydroxylation) and Phase II reactions (conjugation). Glucuronidation, a common Phase II process, produces both active and inactive metabolites.[17] The effectiveness of this metabolism is influenced by hepatic function, blood flow, albumin binding, drug uptake by hepatocytes, hepatocellular integrity, and hepatobiliary system patency. Impairments in these physiological functions can result in accumulation of the parent drug or inadequate formation of necessary metabolites, thereby affecting drug efficacy and toxicity.[18]

IV. CONCLUSION

Long-term use of antiepileptic drugs (AEDs) may contribute to elevated liver enzyme levels, potentially indicating drug-induced liver injury. These elevations can emerge within weeks to months of treatment initiation, depending on the specific type and dosage of the AED. Many first-generation AEDs—such as valproic acid, carbamazepine, and phenytoin—are known for their enzyme-inducing properties, often leading to increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

In contrast, newer-generation AEDs like levetiracetam tend to have a more favorable hepatic safety profile. Research indicates that patients undergoing long-term AED therapy are at increased risk of hepatotoxic side effects, often necessitating regular liver function monitoring. Routine hepatic surveillance is essential, as liver damage is frequently asymptomatic and typically identified only through biochemical testing.

Because liver injury often occurs without overt symptoms, periodic liver enzyme monitoring plays a critical role in the early detection of adverse effects. Such monitoring allows for timely therapeutic adjustments, reducing risk while maintaining effective seizure control. A careful clinical approach is needed, including dosage evaluation and the consideration of safer therapeutic alternatives. Further research is essential to establish clear guidelines on the optimal frequency and methods for liver function monitoring during AED therapy, in order to minimize the risk of transaminitis.

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