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Ketogenic Diet and Drug-Induced Hepatotoxicity During Tuberculosis Treatment

*Francisco Branco Caetano, MD, *Tiago Milheiro Silva, MD, †Cristina Gonçalves, MD, ‡Ana Isabel Dias, MD, *Maria João Brito, MD

Abstract: When therapy with hepatotoxic drugs is being considered, all other possible contributing agents of liver damage should be held to account. While not generally considered a risk factor, we present 2 cases in which ketogenic diet (KD) may have played a role in liver injury due to antituberculosis drugs. Ketogenic diet has been linked to liver injury, and while its pathophysiology remains obscure, carnitine depletion could play a role, as it is a mechanism of liver damage common to KD and antituberculosis drug regimens.

INTRODUCTION

Drug-induced liver injury (DILI) is a frequent complication of most drug regimens, having replaced viral hepatitis as the most common cause of liver failure in adults (1). Known risk factors include use of other hepatotoxic drugs, preexisting liver disease, hepatotropic infections, younger age, and extrapulmonary tuberculosis (TB) (1).

The ketogenic diet (KD) as an antiepileptic therapy is based on the induction of ketosis resulting from free fatty acid β-oxidation, in a protein and carbohydrate restriction context (2). Although uncommon, KD has been linked to liver injury, especially when other potentially hepatotoxic drugs are used simultaneously (3). The precise mechanism through which toxicity occurs has not yet been clarified.

We report 2 cases depicting a rare situation that, to the best of our knowledge, hasn't been described before, aiming to highlight the difficulty of determining specific causes of hepatotoxicity in complex patients receiving multiple drug regimens or diets.

Case Reports

The first case concerns a 7-month-old girl with dug-susceptible miliary TB, affecting the lungs, eye, and the central nervous system, who was treated with isoniazid (10 mg/kg), rifampin (15 mg/kg), ethambutol (20 mg/kg), pyrazinamide (20 mg/kg), prednisolone (1 mg/kg), pyridoxine (15 mg/kg), and levofloxacin (15 mg/kg). She had been diagnosed with development delay and refractory epilepsy due to a cyclin-dependent kinase-like 5 deficiency disorder and medicated with vigabatrin (50 mg/kg) and levetiracetam (25 mg/kg) since she was 3 months old. Due to the worsening of seizure frequency during admission, KD was started along clonazepam (0.07 mg/kg) and topiramate (3 mg/kg); vigabatrin was withheld due to evidence of brain abnormalities on magnetic resonance. She was discharged 47 days later. Transaminase levels at discharge were normal. Three months later, the anti-TB regimen was downscaled to just isoniazid and rifampin (Fig. 1).

During the fourth month of anti-TB treatment with isoniazid, rifampin, and the aforementioned antiepileptic therapy, an asymptomatic 10-fold raise of the transaminases level was detected, prompting suspension of isoniazid and rifampin. The antiepileptic drugs remained unchanged, as well as the ketogenic ratio. Other causes of liver injury, such as viral hepatitis, were excluded. After 10 days, normalization of laboratorial values was attained, leading to an uneventful rechallenge with rifampin and, 3 weeks later, with isoniazid, both at the same dose as initially.

On the sixth month of antibiotic therapy, upon the onset of nausea and vomiting, blood tests revealed a substantial rise of both alanine transaminase (ALT) and aspartate transaminase (AST). There was no cholestasis or liver insufficiency. She was admitted, and antituberculosis drugs were suspended, followed by a normalization of the transaminase levels, after which rifampin and levofloxacin were started, with a 10-day interval. She was then discharged. This time, no isoniazid rechallenge was attempted. No changes were made to the ketogenic ratio or antiepileptic treatment.

A similar episode occurred on the eighth month of therapy. Treatment was suspended and normalization was observed, prompting rechallenge with rifampin. A new rise of transaminases was observed, but at this time, rifampicin was not suspended. The ketogenic ratio was adapted from 3:1 to 2:1, with a gradual restoration of normal transaminase levels.

The patient completed a total of 9 months of antituberculosis therapy with no further complications. Ultimately, clonazepam was successfully withdrawn, while maintaining therapy with levetiracetam and topiramate as well as KD, with normal hepatic tests.

The second case features a 5-year-old boy who was hospitalized with mediastinal tuberculosis. He was suffering from refractory epilepsy associated with alternating hemiparesis and was medicated with phenobarbital (3 mg/kg), zonisamide (5 mg/kg), and clobazam (5 mg) for 8 months, while also on KD for 6 months. Therapy with isoniazid (10 mg/kg), rifampin (15 mg/kg), ethambutol (20 mg/kg), and pyrazinamide (20 mg/kg) was started. On the sixth day of antituberculosis treatment, he presented with lethargy and nausea. His blood tests revealed a substantial rise of both ALT and AST levels (Fig. 2). There was no cholestasis or hepatic insufficiency, and other causes of liver injury, such as viral infections, were excluded. Antituberculosis therapy was suspended, and the antiepileptic drug doses were lowered. KD and ketogenic ration were maintained as refractory epilepsy stability had only been achieved since its implementation.

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From the *Infectious Diseases Unit, Pediatric Department, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal; †Gastroenterology and Hepatology Unit, Pediatric Department, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal; and ‡Neuropediatrics Department, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal.

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Correspondence: Francisco Branco Caetano, MD, Infectious Diseases Unit, Pediatric Department, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Rua Jacinta Marto 8A, 1169-045 Lisboa, Portugal. E-mail: franciscobcaetano@gmail.com

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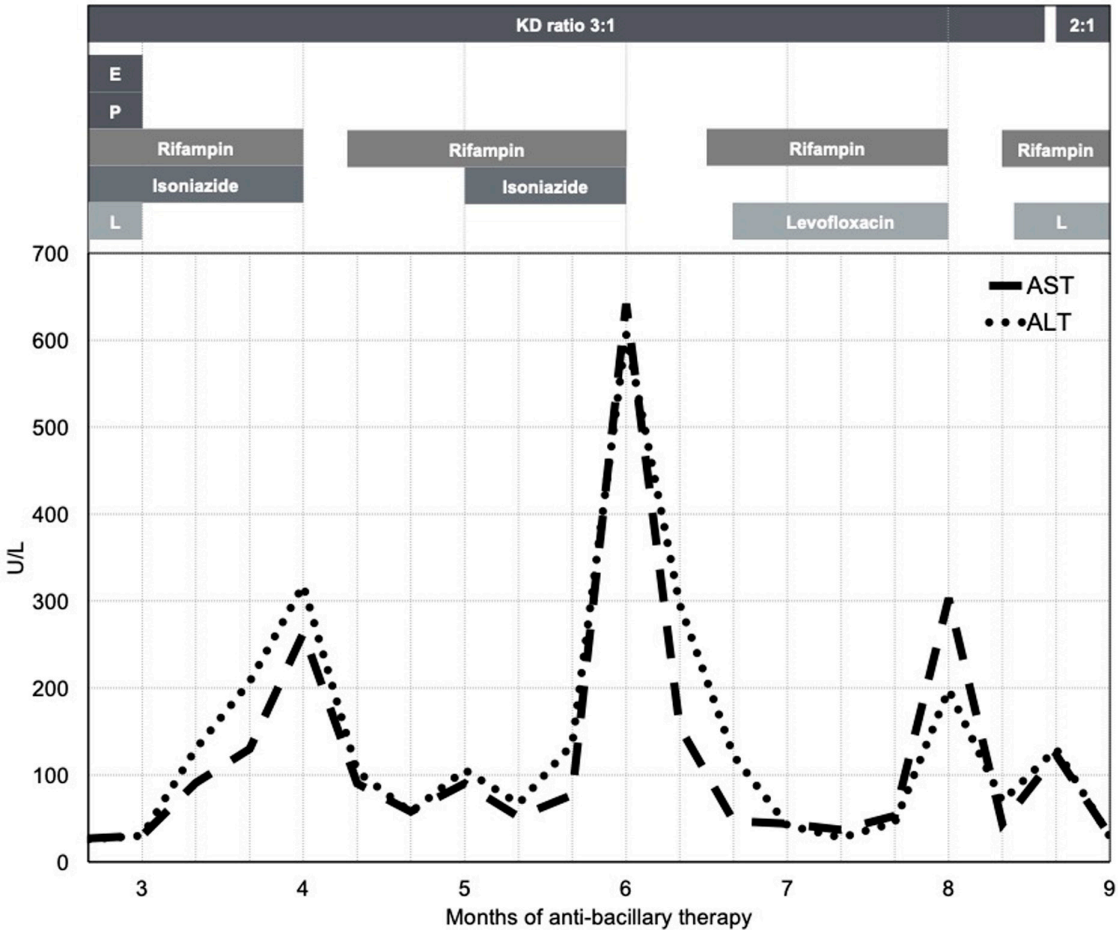

FIGURE 1. Case 1: aminotransferase evolution with relation to therapy. E = Ethambutol; KD = ketogenic diet; L = Levofloxacin; P= Pyrazinamide.

After an initial rise of the transaminase values, steady normalization was observed. The phenobarbital dose was increased after the recrudescence of seizures. Rifampicin and ethambutol were reintroduced simultaneously without complications. After 1 week, isoniazid was introduced, prompting a new asymptomatic 12-fold rise of the aminotransferase levels after 5 days and was once again suspended. After laboratorial normalization, pyrazinamide and levofloxacin (15 mg/kg) were started. This regimen was maintained for 2 months, after which it was downscaled to just rifampin and levofloxacin. He completed 6 months of antituberculosis drugs without further complications.

DISCUSSION

Reintroducing antituberculosis drugs after a toxic event can be distressful since the precise cause is frequently oblivious. In the absence of pediatric guidelines, in both cases, rechallenging schemes as suggested by the American Thoracic Society (1) were employed.

Among others, carnitine depletion has been pointed as a possible mechanism of liver damage during antituberculosis treatment. Carnitine is responsible for the transport of long-chain fatty acids to the mitochondria. Some antiepileptic drugs, such as valproate, use the same metabolic machinery in their β-oxidation process. In a setting of carnitine depletion, this process is shifted toward ω-oxidation, responsible for the production of toxic byproducts (4). Indeed, carnitine supplementation has been shown to significantly decrease the risk of toxic hepatitis during TB treatment (5). The infection itself may play a role as well, through direct hepatic damage and hypercatabolic inflammatory states. Once again, carnitine metabolism dysfunction has been proposed as a pathway, which can, in turn, impair the immune response (6). Lastly, while KD isn't widely considered a risk factor for DILI, it has been independently associated with hypercholesterolemia, hypertriglyceridemia, persistently raised levels of ALT and AST, steatosis, and gallstones through multiple pathways, including carnitine storage depletion (3,7).

In the two cases described, multiple risk factors combined, raising the chances of liver damage, making it hard to single out a unique culprit. In case 1, the timing of transaminase elevation (4 months) was within described time lines, even if it occurred after what is estimated to be the average therapy duration before symptom onset (8). In case 2, toxicity occurred much sooner (6 days). Even though the time between the start of therapy and disease onset is extremely variable, clinical symptoms within the first week of therapy are uncommon (8). The fact that multiple risk factors can contribute to not only raise the chances of DILI but interfere with its most frequent time line can only be guessed.

Although in both cases isoniazid toxicity seems to have occurred, a synergic action between antituberculosis regimen, the antiepileptic drugs, and KD may have been favored by common molecular pathways, leading up to liver dysfunction. Further studies are needed in order to establish definitive causality and to grasp the extent and mechanisms of which KD can contribute to liver damage.

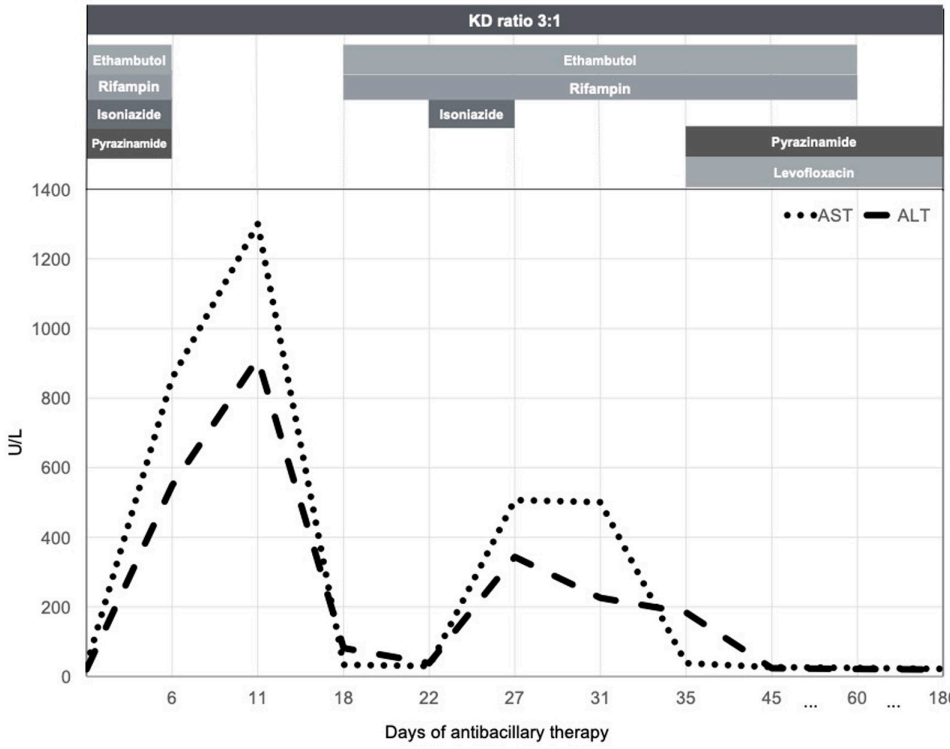

FIGURE 2. Case 2: aminotransferase evolution with relation to therapy. ALT = alanine transaminase; AST = aspartate transaminase; KD = ketogenic diet.

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