Journal of Hepatology and Gastrointestinal Disorders

Kappus at al., J Hepatol Gastroint Dis 2017, 3:1
DOI: 10.4172/2475-3181.1000141

Case Report Open Access

Liver Transplantation for the Management of Acute Intermittent Porphyria: A Case Report

Matthew R Kappus[1], **Bryant B Summers**[2], **Jennifer S Byrns**[2*], **Carl L Berg**[1] **and Julius M Wilder**[1]

[1]*Division of Gastroenterology, Duke University School of Medicine, Durham NC, United States*

[2]*Department of Pharmacy, Duke University Hospital, Durham NC, United States*

[*]**Corresponding author:** Jennifer S Byrns, Department of Pharmacy, Duke University Hospital, DUMC BOX 3089, Durham, NC 27710, United States, Tel: 919-681-0677; E-mail: Jennifer.byrns@duke.edu

Received date: December 27, 2016; **Accepted date:** January 16, 2017; **Published date:** January 20, 2017

Abstract

We report a single patient with acute intermittent porphyria whose porphyria was successfully treated with orthotopic liver transplantation. She had a very poor quality of life as a result of years of frequent acute porphyria symptoms manifesting as abdominal pain crises. After transplantation, clinical signs of porphyria resolved as expected. This case adds to a growing body of literature which is assisting to formulate the indications for, and the timing of, transplantation for AIP.

Keywords: Liver transplant; Porphyria; Outcomes; Safety

Introduction

Acute intermittent porphyria (AIP) is characterized by insufficient hydroxymethylbilane synthase activity, also known as porphobilinogen deaminase (PBGD), which is responsible for synthesizing the substrate porphobilinogen (PBG). The neurotoxic agents of AIP, PBG and 5-aminolevulinic acid (ALA), are found in high concentrations in the plasma and urine in patients with AIP. Patients with AIP suffer from episodic attacks of abdominal and neurologic symptoms. Attacks may be frequent, severe, and potentially life-threatening. Liver transplantation (LT) has been successfully used for treatment of AIP [1]. The genetic defect resulting in PBGD deficiency and porphyrin accumulation is corrected by transplantation using a liver with normal PBGD activity.

Case Report

A 30 year old female with a longstanding diagnosis of AIP presented to our transplant center for consideration of orthotopic LT. She was diagnosed at 16 years of age, confirmed by a c517C>T exon T mutation in the PBGD-gene. At the time of her diagnosis, transplantation had been recommended, and she reports innumerable hospital admissions during the first two years after her diagnosis. In the following years, she required weekly hematin infusions, which caused significant fatigue and lethargy, as well as bimonthly phlebotomies to manage the resultant hyperferritinemia from her constant heme infusions. Her need for frequent hospitalization, pronounced fatigue, and debilitating abdominal pain prompted the decision to explore LT for a potential cure.

She was evaluated at our center two years prior to transplant at a time of clinical stability. Prior to transplant, her urinary PBG excretion was 269.7 mcmol/l, consistent with the diagnosis of AIP. She also had a serum ferritin of 327 ng/ml, iron of 23 mcg/dl, and percent iron saturation of 4% (in the setting of regular phlebotomy). After receiving approval, transplantation was performed with split liver right lobe with middle hepatic vein and standard arterial anatomy. Her surgery was uncomplicated and she received empiric antibiotic coverage perioperatively including micafungin and piperacillin-tazobactam. Fluconazole is typically used at our transplant center, but was avoided given her history of AIP, and uncertainty regarding kinetics of her PBG and ALA clearance immediately postoperatively. Her postoperative course was complicated by acute kidney injury felt to be pre-renal azotemia secondary to acute tubular necrosis from surgery and improved with intravenous hydration. She also had lactic acidosis with serum lactate as high as 7.6 in the immediate postoperative period which improved with fluid resuscitation and respiratory management. Standard immunosuppressant therapy was used including tacrolimus, mycophenolate mofetil, and prednisone. Nebulized pentamidine, rather than sulfamethoxazole-trimethoprim, was used for pneumocystis pneumonia prophylaxis to decrease risk for potential exacerbation. Based on a reported higher rate of hepatic artery thrombosis (HAT) in patients with AIP who have undergone LT, the patient was started on therapeutic enoxaparin for a total of 9 months of treatment [2]. Nine months after transplant, she has no clinical or biochemical signs of porphyria, normal graft function (liver function tests included alanine aminotransferase 9 U/L, aspartate aminotransferase 13 U/L, alkaline phosphatase 26 U/L, total bilirubin 0.2 mg/dl, albumin 4.4 g/dl), and reported improved quality of life. The patient's ferritin also normalized as quickly as 1 month after transplant to 218.1 ng/ml (down from 355 ng/ml pre-transplant).

Discussion

AIP results from an autosomal dominant mutation that leads to a deficiency in the production of PBGD, which is a critical enzyme involved in the heme synthesis pathway [3,4]. The increased demand for heme leads to an overproduction of ALA synthase which forms PBG, a porphyrin precursor. Accumulation of porphyrin precursors when coupled with activating factors such as medications, nutritional changes, infections, and hormonal changes can cause acute attacks [5]. Attacks are characterized by abdominal pain, sympathetic over-activity resulting in tachycardia, hypertension, tremors, diaphoresis, arrhythmias, and acute neurologic manifestations (confusion,

hallucinations, neuropathy, and seizures) [1]. Treatment for AIP is limited to avoidance of precipitating factors and/or receiving intermittent infusions of hematin, an exogenous source of heme [6].

Recurrent AIP attacks can affect patient's quality of life. LT gives patients the potential for cure through improvement in heme synthesis within the liver [7]. The remaining PBGD deficiency in extra-hepatic tissues lacks clinical relevance after transplant. Review of the available literature yields a reported 14 LT's for treatment of AIP. 1 LT in AIP should be considered last resort when other therapies have failed. While difficult to weigh the risks and benefits, LT should be considered before complicating or contraindicating factors arise. Our patient chose to purse transplantation before the natural course of AIP jeopardized the option for transplant. It is reasonable to argue that LT should be limited to patients with recurrent severe attacks or an anticipated risk for severe consequences such as severe neurologic symptoms, chronic hypertension, progressive neuropathy, or hepatocellular carcinoma. A retrospective study performed in the UK described the outcome of LT in 10 patients (median age: 31 years [range 18 years to 50 years]; 9 females) with AIP and recurrent neurovisceral attacks and poor quality of life. Clinical and biochemical remission occurred in all patients, with PBG and ALA levels returning to normal within 24 h to 72 h [2].

When transplantation is pursued to cure AIP, several unique issues should be considered. First are medications used during the transplant course. Several medication classes can precipitate acute attacks via induction of ALA synthase and the cytochrome P450 enzyme systems, which lower the pool of hepatic heme leading to a feedback stimulation that increases porphyrin production [1,8-10]. Most immunosuppressant and infection prophylaxis medications are considered safe, with the exception of sulfonamides [4]. Medication selection can be guided by use of safety data available through porphyria foundations and organizations.

The second unique issue for transplantation and AIP is the risk of HAT. A previously published review reported an incidence of HAT of 40% (4 out of 10 patients) with development early at 30 days out to 9 months [7]. Due to the increased incidence of HAT in AIP patients following transplant, we suggest use of anticoagulation postoperatively [2]. Our patient was prescribed prophylaxis with enoxaparin as well as low dose aspirin for the first 9 months post-transplantation.

The third issue which may come up in the setting of transplantation for AIP, is that the native liver from the transplant recipient may not be transplanted into another patient. Previous experience with "domino" liver transplants have shown that livers from donors with AIP can develop acute attacks associated with accumulation of porphyrin precursors and recipients will potentially go on to develop AIP [2].

References

1. Singal AK, Parker C, Bowden C, Thapar M, Liu L, et al. (2014) Liver transplantation in the management of porphyria. Hepatology 60: 1082-1089.
2. Dowman JK, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, et al. (2012) Liver selection and allocation working party. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transpl 18: 195-200.
3. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, et al. (2005) Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med 142: 439-450.
4. Khanderia U, Bhattacharya A (1984) Acute intermittent porphyria: pathophysiology and treatment. Pharmacotherapy 4: 144-150.
5. Seth AK, Badminton MN, Mirza D, Russell S, Elias E (2007) Liver transplantation for porphyria: who, when, and how? Liver Transpl 13: 1219-1227.
6. Bissell DM (1988) Treatment of acute hepatic porphyria with hematin. J Hepatol 6: 1-7.
7. Soonawalla ZF, Orug T, Badminton MN, Elder GH, Rhodes JM, et al. (2004) Liver transplantation as a cure for acute intermittent porphyria. Lancet 363: 705-706.
8. Thunell S, Pomp E, Brun A (2007) Guide to drug porphyrogenicity prediction and drug prescription in the acute porphyrias. Br J Clin Pharmacol 64: 668-679.
9. Bissell DM, Wang B (2015) Acute hepatic porphyria. J Clin Transl Hepatol 3: 17-26.
10. Hahn M, Gildemeister OS, Krauss GL, Pepe JA, Lambrecht RW, et al. (1997) Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells: potential implications for patients with acute porphyria. Neurology 49: 97-106.
11. Telkes G, Pusztai A, Foldes K, Langer RM (2013) Kidney transplantation in hereditary coproporphyria using tacrolimus and mycophenolate mofetil: a case report. Transplant Proc 45: 3703-3704.
12. Barone GW, Gurley BJ, Anderson KE, Ketel BL, Abul-Ezz SR (2001) The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. J Clin Pharmacol 41: 113-115.