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Combined Liver and Kidney Transplant in Acute Intermittent Porphyria: A Case Report

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Patient: Male, 19-year-old
Final Diagnosis: Acute intermittent porphyria
Symptoms: Abdominal pain • dark color urine • weakness
Medication: —
Clinical Procedure: Kidney transplantation • liver transplantation
Specialty: Gastroenterology and Hepatology • Hematology • Nephrology • Surgery • Transplantology

Objective: Rare disease

Background: Acute intermittent porphyria is an inherited disease caused by a defect in heme biosynthesis, with accumulation of neurotoxic metabolites leading to acute neurovisceral symptoms. Some patients develop long-term neurological and renal damage after the acute episodes, many of them requiring hemodialysis. Since heme production in the human body occurs predominantly in the bone marrow and liver, liver transplantation has been shown to significantly reduce the production of neurotoxic metabolites, effectively controlling the disease. Patients with severe acute intermittent porphyria who have chronic kidney failure may benefit from combined kidney and liver transplant. Only 2 uses of this approach have been previously reported in the literature.

Case Report: We report here the case of a 19-year-old male patient who received a combined liver and kidney transplant for the treatment of acute intermittent porphyria. He presented the first symptoms of the disease 4 years before the procedure, with abdominal pain and significant neurological impairment, with weakness requiring prolonged mechanical ventilation. He also had chronic kidney failure secondary to the porphyria. A combined liver and kidney transplant was performed, with no intraoperative complications. The explanted liver showed light siderosis, as well as portal and perisinusoidal fibrosis at microscopy. At 3.5 years of follow-up, he remains clinically well, with normal hepatic and renal function, had had no further acute porphyria episodes, and shows progressive neurological recovery.

Conclusions: This case demonstrates that combined liver and kidney transplant can be a curative treatment for patients with severe acute intermittent porphyria associated with end-stage renal failure. The patient shows satisfactory long-term function of both grafts, with no clinical or biochemical signs of porphyria recurrence.

MeSH Keywords: Hematologic Diseases • Kidney Transplantation • Liver Transplantation • Porphyria, Acute Intermittent • Porphyrias • Renal Insufficiency

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Background

Acute intermittent porphyria (AIP) is an inherited disease caused by a defect in heme biosynthesis, leading to acute neurovisceral symptoms. Heme is an iron-based molecule that functions as an essential cofactor for a number of proteins in the human body, such as hemoglobin, myoglobin, and cytochromes P-450. Heme is synthetized in many different tissues, but most of the production occurs in the bone marrow and the liver [1]. AIP is one of the 4 acute hepatic porphyrias, a group of diseases that comprises: 5-aminolevulinic acid dehydratase deficiency porphyria, AIP, hereditary coproporphyria, and variegate porphyria [1]. AIP is both the most severe and the most common of them, with an estimated prevalence of 5 in 1600 people for the mutation, of which only 2% will develop symptoms during their lifetime, reflecting a key role of environmental factors and, possibly, genetic modifiers [1,2].

A genetic mutation in the hydroxymethylbilane synthesis gene causes a partial deficiency in activity of the porphobilinogen deaminase enzyme, leading to the accumulation of the neurotoxic upstream metabolites aminolevulinic acid (ALA) and porphobilinogen [2–4].

Symptomatic disease is more common in females, and usually manifests between 15 and 50 years of age. Acute episodes are characterized by diffuse abdominal pain, usually of a colicky nature, associated with constipation, nausea, vomiting, and weakness [1,2]. Other common symptoms are hypertension, tachycardia, and dark-colored urine. Freshly voided urine in patients with AIP appears unremarkable, as ALA and porphobilinogen are colorless. However, if exposed to light, it will slowly assume a dark color, as the oxidation of porphobilinogen in urine leads to the formation of a dark brown pigment [1,2,4]. Neurological symptoms consist mostly of proximal weakness and hyperesthesia, but seizures, bulbar paralysis, dysphagia, and dysarthria may also occur. Neuropsychiatric manifestations are attributed to the structural similarities between ALA and gamma-aminobutyric acid, a major neurotransmitter, and also to a direct toxic effect of ALA [1,2]. AIP can be diagnosed by the measurement of urinary ALA and porphobilinogen, which remain elevated for several days after an acute attack [1]. Common triggers for acute porphyria attacks include infections, prolonged fasting, progesterone, alcohol intake, physical or emotional distress, and certain drugs (e.g., sulfonamides, benzodiazepines, and valproate) [1,2].

The initial treatment of acute AIP episodes includes carbohydrate administration (usually intravenous 10% dextrose), analgesics, and intravenous hematin infusion. Heme infusion works by a negative feedback mechanism, reducing the activity of the defective enzymes in the heme synthesis process and thereby decreasing the production of toxic metabolites [2]. Patients with frequent symptoms may receive weekly prophylactic hematin infusions.

Renal pathology in AIP is caused mainly by ALA, which is particularly nephrotoxic, causing oxidative damage to the mitochondrial membrane of convoluted proximal tubule cells and leading to chronic tubule-interstitial nephropathy and focal cortical atrophy [4–6]. Hypertension during the acute episodes can also contribute to kidney damage. Arteriolopathy can also play a role, as both ALA and porphobilinogen are apoptosis inducers and show *in vitro* vascular toxicity [7,8]. Some patients progress to chronic kidney failure after having acute porphyria attacks [4–8]. There are reports that hemodialysis can worsen neuropathy symptoms in these patients, as ALA and porphobilinogen levels can increase after dialysis [9,10]. Kidney transplant has been successfully used to treat patients with chronic renal failure secondary to AIP [11–13]. While there is some concern in the choice of immunosuppressive drugs in patients with AIP after the kidney transplant, the use of calcineurin inhibitors, such as cyclosporine and tacrolimus, is generally considered to be safe [11].

Studies show a marked increase in the risk of hepatocellular carcinoma in patients with AIP, particularly after 50 years of age [4,14,15]. It is possible that heme deficiency and the increase in ALA levels lead to the production of reactive oxygen species in the liver, creating a carcinogenic microenvironment [14].

Since the liver is one of the major sites of heme production in the human body, liver transplantation leads to a significant reduction in the synthesis of toxic metabolites in patients with AIP, neutralizing the risk of acute porphyria attacks [16]. Patients with severe, intractable, and disabling attacks that are refractory to hematin infusion can therefore be considered for orthotopic liver transplantation, which has been shown to be a curative procedure in AIP [1,2,17].

Two cases of combined liver and kidney transplant in patients with AIP were reported in Sweden. Both patients had chronic kidney failure secondary to AIP, and showed excellent recovery after the transplant [9].

Case Report

A male patient had acute episodes of diffuse abdominal pain, associated with nausea and vomiting, lasting from 12 h to 2 days, occurring approximately every 3–6 months, and improving after medication with intravenous analgesics. The symptoms started when he was 15 years old. The patient had no significant comorbidities. His past medical history was uneventful, with no past surgeries or hospital admissions. He had no family history of

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kidney or liver disease. He presented several times to the emergency room of a hospital in his home city in the northeastern region of Brazil, where he was discharged every time after his symptoms improved with intravenous medication. Initial laboratory and radiologic exams were normal, and he received no definite diagnosis for the cause his symptoms. Two years after the onset of the symptoms, he had a new episode of fever, odynophagia, abdominal pain, and dark-colored urine. He had laboratorial markers of acute kidney failure and was admitted to the hospital. He was transferred to a tertiary hospital in a different part of the country, and hemodialysis was initiated due to progressive worsening of his renal function. The patient had not used any potentially nephrotoxic medication, such as nonsteroidal anti-inflammatory drugs, in the 6 months prior to this episode. Screening for possible causes of kidney injury included testing for rheumatoid factor, antinuclear antibodies, complement components (C3 and C4), thyroid stimulating hormone, anti-cyclic citrullinated peptide, anti-cardiolipins, lupus anticoagulant, anti-neutrophil cytoplasmic antibody, and anti-Ro and anti-La antibodies, all of which yielded unremarkable results.

After being prescribed diazepam to reduce anxiety during dialysis, he developed peripheral muscle weakness, with progressive deterioration leading to involvement of the respiratory muscles. Endotracheal intubation and mechanical ventilation were necessary due to respiratory failure. Due to prolonged endotracheal intubation, a gastrostomy and a tracheostomy were performed. Acute intermittent porphyria was suspected, and a urine sample was positive for porphobilinogen and showed elevated levels of ALA, with 6.7 mg per gram of creatinine (the maximum reference level is 4.5 mg/g creatinine). After the suspension of all drugs that could possibly act as a trigger for AIP attacks (metoclopramide, benzodiazepines, and phenytoin), the patient showed slow improvement of his weakness, with successful weaning from mechanical ventilation, and a return to oral feeding and ambulation. He remained hospitalized for 183 days, with 110 days of those being in the intensive care unit. He showed no improvement of his renal function, however, and hemodialysis on alternate days in an outpatient clinic was necessary. A second urinary exam for ALA and porphobilinogen was performed, with results similar to the first one. Genetic testing of the patient and his immediate family revealed an IVS9–1G >A intronic mutation in the PBGD gene in the patient and his father, who was asymptomatic. This mutation has a significant association with AIP.

He consulted in a liver and kidney transplant unit 1 year after hospital discharge, with persistent weakness and chronic kidney failure. While he had no further episodes of abdominal pain or infection during this 1-year period, there were no signs of kidney function recovery, with persistently elevated urea and creatinine levels and minimal diuresis. The first symptoms of AIP had started 3 years before his referral, and he was receiving hemodialysis for 18 months.

At examination, the patient showed proximal and distal weakness in all 4 limbs, was unable to write or perform other tasks requiring fine motor skills, and had a characteristic myopathic gait and moderate dysarthria, causing a reduction in speech intelligibility. He had no increase in aminotransferases or any clinical or laboratorial signs of hepatic dysfunction, and a model for end-stage liver disease (MELD) score of 21, largely due to his elevated creatinine (5.1 mg/dl). An ultrasound of the liver with Doppler evaluation of the hepatic and iliac vessels was obtained, with normal results.

After being on the waitlist for 6 months, at age 19 he received a combined liver and kidney transplant from a cadaveric donor. The donor was a 13-year-old male who suffered brain death due to hypoxic injury secondary to an asthma attack. An orthotopic liver transplant was performed, with simultaneous portal and hepatic artery reperfusion of the graft, and a total ischemia time of 313 min. A kidney transplant was performed immediately afterwards, with a cold ischemia time of 478 min. There were no intraoperative complications, and the patient received no blood product transfusion. He received induction immunosuppressive therapy with 3 mg/kg of thymoglobulin, administered on the 2 first post-operative days (POD). On the first POD he also started using 100 mg of methylprednisolone, with gradual tapering of the dose, 8 mg of tacrolimus, 1440 mg of mycophenolate mofetil, and prophylactic subcutaneous heparin. He received 4 sessions of hemodialysis, from the first to the fifth POD, after which he demonstrated a progressive increase in diuresis and a decrease in creatinine and urea levels. He was discharged from the hospital in the ninth POD, using prophylactic acetylsalicylic acid.

Nineteen days after the procedure, a new urinary sample was obtained and tested for porphobilinogen, which was negative, and ALA levels, which had decreased to 0.8 mg/g creatinine. Microscopy of the explanted liver showed light siderosis, as well as portal and perisinusoidal fibrosis. At 1 and 5 months after the transplant, he had 2 episodes of cytomegalovirus reactivation detected by antigenemia and treated with ganciclovir and reduction of the immunosuppressive regimen. He currently attends a rehabilitation program and showed significant improvement of his muscular weakness, being able to write, walk normally, and speak with greater intelligibility. At 42 months after the procedure, he remains with adequate function of both liver and kidney grafts, has had no episodes of rejection or further acute AIP attacks, and receives a triple immunosuppressive drug regimen consisting of tacrolimus, everolimus, and prednisone.

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Discussion

Diagnosis of AIP can be challenging, with patients often suffering multiple acute episodes before adequate treatment is initiated. Clinical treatment consists in the avoidance of common triggers for porphyria attacks, and in the infusion of intravenous hematin. Hematin treatment can be costly, and phlebitis of peripheral vessels or the requirement for a central venous catheter causes a negative long-term impact in the quality of life of these patients. Approximately 5–10% of patients show no adequate response to hematin therapy, and disease progression in those cases may lead to significant neurological and renal damage [17]. Liver transplantation is a curative treatment for AIP, restoring normal excretion of ALA and porphobilinogen, preventing acute porphyria attacks, and preventing the development of further disabilities, and should be considered in those patients who do not respond or adapt adequately to hematin treatment [17–20].

More than a dozen liver transplants for patients with severe AIP have been reported, with clinical and biochemical remission in all cases and normalization of ALA and porphobilinogen levels within 72 h [16,18]. Survival is similar to that of liver transplantation performed for other indications [16,19,20]. Some studies report an increase in the occurrence of hepatic artery thrombosis in patients who received liver transplantation for the treatment of AIP [19]. This may be related to the administration of hematin before the procedure, since hematin can cause platelet aggregation after its infusion [4]. The use of anticoagulation or antiplatelet therapy is generally recommended after liver transplantation for AIP [18,21]. The explanted livers are usually unremarkable, except for moderate siderosis and steatosis, but detailed studies have described the presence of nodular regenerative hyperplasia and focal incomplete septal cirrhosis in some cases, suggesting that even patients with no clinical or laboratory markers of liver disease may have a greater amount of liver damage than previously imagined [22].

In patients with chronic kidney failure secondary to AIP, kidney transplantation offers a cure for the renal dysfunction, but has no impact on the natural history of AIP. The patients remain at risk for new porphyria attacks, with possible worsening of neurological symptoms and deterioration of graft function.

Combined liver and kidney transplant is a particularly beneficial treatment option in these patients, as it not only restores kidney function, but also protects the patient from new acute episodes of AIP. In the 2 cases previously reported in the literature, 2 female patients (a 55-year-old and a 24-year-old) had complete remission of AIP symptoms and adequate liver and kidney graft function in a follow-up period of 16 months [9].

Since normalization of ALA and porphobilinogen levels occurs shortly after the patient receives the liver transplant, we saw no need for withholding the use of drugs that commonly act as triggers for AIP attacks, such as sulfamethoxazole or corticosteroids, in the post-operative management of this patient.

To reduce the risk of hepatic artery thrombosis that has been described in other reports of liver transplant in AIP, we did not administer intravenous hematin immediately before the procedure. We also administered heparin prophylaxis during inpatient care, substituted by acetylsalicylic acid at the time of hospital discharge. Despite having normal laboratory markers of liver function before the transplant, the liver explanted from our patient showed portal and perisinusoidal fibrosis, which raises concern for the potential use of organs obtained from AIP patients in sequential domino liver transplants. In the present case, we have observed the potential for long-term recovery of neurological symptoms such as weakness and dysarthria after the transplant.

Conclusions

Combined liver and kidney transplant is a safe and effective treatment for patients with chronic kidney failure secondary to AIP. It should be considered as an alternative when there is no satisfactory response to first-line treatments such as hematin therapy. It can prevent further episodes of porphyria attacks, restore kidney function, and allow progressive recovery from previous neurological damage.

Conflicts of interest

None.

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References:

1. Wang B, Rudnick S, Cengia B, Bonkovsky HL: Acute hepatic porphyrias: Review and recent progress. Hepatol Commun, 2019; 3(2): 193–207
2. Spiritos Z, Salvador S, Mosquera D, Wilder J: Acute intermittent porphyria: Current perspectives and case presentation. therapeutics and clinical risk management. 2019; 15: 1443–51
3. Dhital R, Basnet S, Poudel DR, Bhusal KR: Acute intermittent porphyria: A test of clinical acumen. J Community Hosp Intern Med Perspect, 2017; 7(2): 100–2
4. Bissell DM, Anderson KE, Bonkovsky HL: Porphyria. N Engl J Med, 2017; 377(9): 862–73
5. El-Haggan W, Lobbedez T, Ryckelynck JP, Ligny BH: Sirolimus tolerability in a kidney transplant recipient with acute intermittent porphyria. Nephrol Dial Transplant, 2002; 17: 1147
6. Marsden JT, Chowdhury P, Wang J et al: Acute intermittent porphyria and chronic renal failure. Clin Nephrol, 2008; 69(5): 339–46
7. Andersson C, Wikberg A, Stegmayr B, Lithner F: Renal symptomatology in patients with acute intermittent porphyria. A population-based study. J Intern Med, 2000; 248: 319–25
8. Pallet N, Mami I, Schmitt C et al: High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. Kidney Int, 2015; 88: 386–95
9. Wahlin S, Harper P, Sard E et al: Combined liver and kidney transplantation in acute intermittent porphyria. Transpl Int, 2010; 23: e18–21
10. Unzu C, Sampedro A, Sardh E et al: Renal failure affects the enzymatic activities of the three first steps in hepatic heme biosynthesis in the acute intermittent porphyria mouse. PLos One, 2012: 7(3): e32978
11. Warholm C, Wilczek H: Renal transplantation in a case of acute intermittent porphyria. J Clin Pharmacol, 2003; 43: 1158–60
12. Alfano G, Ventura P, Fontana F et al: *Rhodococcus equi* pneumonia in kidney transplant recipient affected by acute intermittent porphyria: A case report. Transplant Proc, 2019; 51(1): 229–34
13. Warholm C, Wilczek H: Renal transplantation in a case of acute intermittent porphyria. J Clin Pharmacol, 2003; 43(10): 1158–60
14. Sardh E, Wahlin S, Bjornstedt M, Harper P, Andersson DEH: High risk of primary liver cancer in a cohort of 179 patients with Acute Hepatic Porphyria. J Inherit Metab Dis, 2013; 36: 1063–71
15. Andant C, Puy H, Bogard C et al: Hepatocellular carcinoma in patients with acute hepatic porphyria: frequency of occurrence and related factors. J Hepatol, 2000; 32: 933–39
16. Singal AK, Parker C, Bowden C et al: Liver transplantation in the management of porphyria. Hepatology, 2014; 60(3): 1082–90
17. Soonawalla ZF, Orug T, Badminton MN et al: Liver transplantation as a cure for acute intermittent porphyria. Lancet, 2004; 363: 705–6
18. Malinzak EB, Kudsen NW, Udani AD et al: Perioperative challenges in liver transplantation for a patient with acute intermittent porphyria. J Cardiothorac Vasc Anesth, 2017; 32(6): 2716–20
19. Downman JK, Gunson BK, Mirza DF et al: Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transplantation, 2012; 18: 195–200
20. Seth AK, Badminton MN, Mirza D et al: Liver transplantation for porphyria: Who, when, and how? Liver Transpl, 2007; 13: 1219–27
21. Kappus MR, Summers BB, Byrns JS et al: Liver transplantation for the management of acute intermittent porphyria: A case report. Journal of Hepatology and Gastrointestinal Disorders, 2017; 3(1): 1000141
22. Yasuda M, Erwin AL, Liu LU et al: Liver transplantation for acute intermittent porphyria: Biochemical and pathologic studies of the explanted liver. Mol Med, 2015; 21: 487–95

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