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CASE REPORT

Combined liver and kidney transplantation in acute intermittent porphyria

Staffan Wahlin,[1] Pauline Harper,[2] Eliane Sardh,[3] Christer Andersson,[4] Dan EH Andersson[3] and Bo-Göran Ericzon[5]

1 Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
2 Department of Laboratory Medicine, Porphyria Centre Sweden, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
3 Department of Internal Medicine, Karolinska Institutet, Stockholm South Hospital, Stockholm, Sweden
4 Department of Public Health and Clinical Medicine, University Hospital, Umeå, Sweden
5 Division of Transplantation Surgery, Karolinska Institutet, Karolinska University Hospital, Huddinge, Stockholm, Sweden

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Correspondence
Staffan Wahlin MD, Department of Gastroenterology and Hepatology, K63, Karolinska Institutet, Karolinska University Hospital, Huddinge, SE-141 86 Stockholm, Sweden. Tel.: +46858587984; fax: +46858582335; e-mail: staffan.wahlin@karolinska.se

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Summary

We report two patients with acute intermittent porphyria (AIP) who were successfully treated with combined liver and kidney transplantation. Both had a very poor quality of life as a result of years of frequent acute porphyria symptoms, chronic peripheral neuropathy and renal failure requiring dialysis. After transplantation, clinical and biochemical signs of porphyria disappeared. The excretion pattern of porphyrin precursors normalized within the first day and plasma porphyrins returned to normal within a week. These and other recent cases have clarified previous concerns and have helped to formulate the indications for and the timing of transplantation in AIP.

Introduction

Acute intermittent porphyria (AIP) is characterized by insufficient hydroxymethylbilane synthase activity (also known as porphobilinogen deaminase; PBGD). Under conditions of forceful induction of hepatic heme synthesis, hepatic PBGD becomes overloaded by its substrate porphobilinogen (PBG). Both PBG and the substrate of the previous enzyme, 5-aminolevulinic acid (ALA), the presumably neurotoxic metabolites in AIP, are found in high concentrations in plasma and urine [1]. AIP is characterized by episodic attacks with abdominal and neurologic symptoms. In some patients, attacks are frequent, severe and potentially life-threatening. Long-term complications include neurologic damage, renal impairment, chronic hypertension and hepatocellular carcinoma [2–6].

A successful liver transplant for severe AIP, reported in 2004 [7], indicated that liver transplantation may be a curative option in AIP. The experience from liver transplantation in AIP is growing [8] and may enable some conclusions to be drawn. Uneventful kidney transplantation alone has been reported in a number of AIP patients [9–11]. This report is the first on combined liver–kidney transplantation (CLKT).

Patients

Case 1

This 24-year-old woman was diagnosed with AIP in 2004 after many years of symptoms and a year of frequent hospitalizations as a result of abdominal pain, hypertensive crises and neuropathy causing the need for noninvasive

ventilator support. A 104-105insGTCT mutation was found in the PBGD-gene. At diagnosis, her renal function was already impaired with an estimated glomerular filtration rate (GFR) of 14.7 ml/min (normal >90 ml/min). She slowly regained most of her motor functions during a year of neurologic rehabilitation. In the following years, she required very frequent hospitalizations for porphyria symptoms. Preventive treatments [12] offered little amelioration. Several attacks were associated with arterial hypertension up to 260/140 mmHg that responded poorly to treatment. Following an attack in 2007, she developed extremity paresis with a transient need for a wheel chair, bulbar paresis with speech difficulties and marked weight loss. Her renal impairment continued to progress, eventually requiring hemodialysis. On dialysis, her plasma porphyrins rose to >1000 nmol/l (normal <10) [13] without causing porphyria-related skin problems.

Her need for frequent hospital care, pronounced neuropathy and hemodialysis prompted the decision to explore liver–kidney transplantation for a potential cure. Plans for transplantation were started when she had regained independent mobility. Transplantation was done by standard techniques. Both surgery and the postoperative period were uncomplicated. Immunosuppression was achieved with tacrolimus, mycophenolate mofetil and prednisolone. Nebulized pentamidine, rather than sulfamethoxazole-trimethoprim, was used for pneumocystis pneumonia prophylaxis. The rationale for this choice was the theoretical risk for aggravation of neuropathy resulting from the still present PBGD deficiency in nerve tissue. By contrast, known porphyrogenic drugs such as nitrofurantoin and possibly porphyrogenic drugs such as tigecycline and linezolid were used without any clinical signs of harm.

Sixteen months later, she still has no clinical or biochemical signs of porphyria. Graft function is normal. She exhibits no clinical signs of neuropathy apart from a slight remaining quadriceps weakness. Figure 1a and b displays the pre- and postoperative pattern of urinary porphyrin precursors and plasma porphyrins.

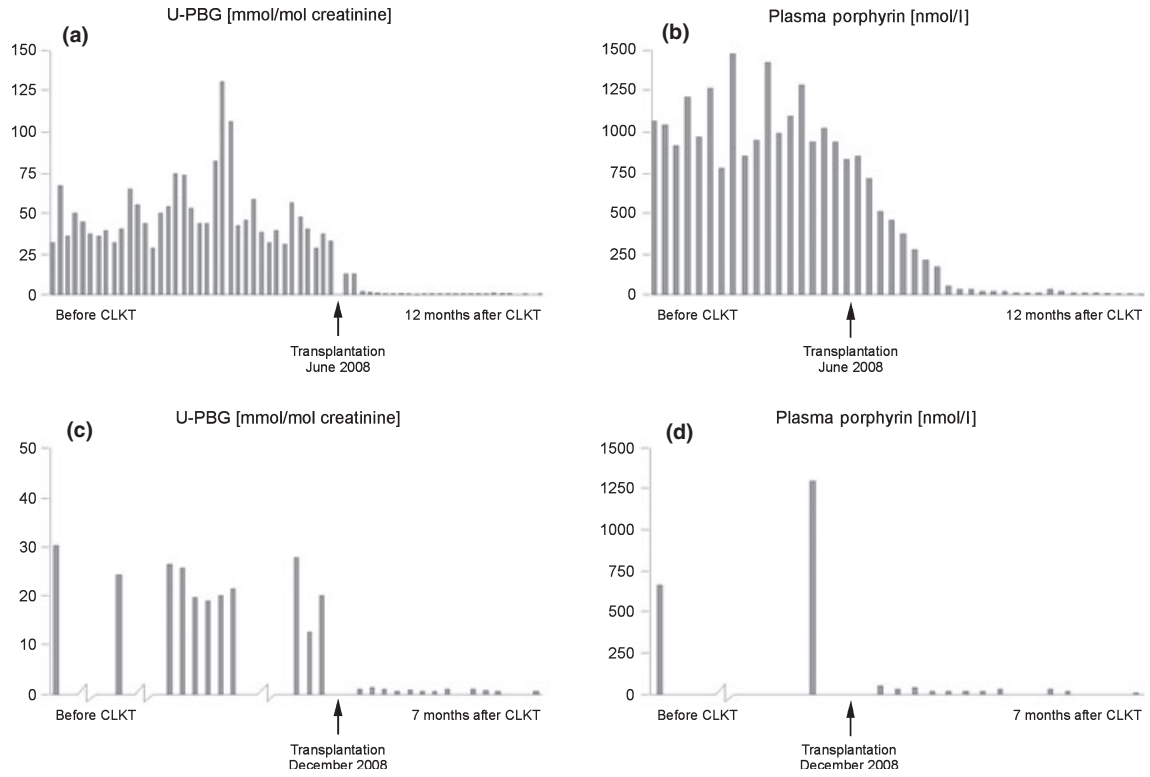

Figure 1 Urinary porphobilinogen (PBG) excretion and plasma porphyrin levels before and after combined liver–kidney transplantation in case 1 (a–b) and case 2 (c–d). The *x*-axis represents serial samples but is not proportionate to time. Major time gaps are indicated by a broken line. U-PBG (normal 1.6 mmol/mol creatinine) normalized within 24 h after transplantation in both cases. The plasma porphyrin levels, mainly uroporphyrin-I, rose to >1000 nmol/l (normal <10) after start of hemodialysis in case 1 and peritoneal dialysis in case 2. This increase may reflect nonenzymatic polymerization of PBG. Plasma porphyrin levels returned to normal within a week after transplantation as clearly illustrated in case 1 (b). Fifteen and 10 months after transplantation, urinary PBG and plasma porphyrin remain at normal levels in both patients. (PBG: Porphobilinogen, CLKT: combined liver–kidney transplantation).

Case 2

This 55-year-old woman was diagnosed with AIP at the age of 21. She carries a 593G>A (W198X) mutation in the PBGD gene. In the last decade, worsening symptoms resulted in frequent hospitalizations. She displayed neuropathy, which progressed independently of the acute porphyria attacks. Her neuropathy included paresthesias in the lower extremities and hands, balance impairment and severe neuropathic pains. Concurrent progressive renal impairment eventually required peritoneal dialysis. Within the first 2 years of dialysis, her plasma porphyrin concentration rose to >1000 nmol/l, causing secondary cutaneous lesions. Her estimated GFR was 6.2 ml/min immediately prior to transplantation.

The same combination of factors as for the case 1 presented a clear indication for combined liver and kidney transplantation. Transplant surgery and postoperative care was uncomplicated except for bile leakage resolved by surgery and a renal rejection episode. She received the same immunosuppression and pneumocystis pneumonia prophylaxis as case 1.

Eleven months after transplantation, there are no signs of porphyria, graft function is normal and all clinical manifestations of neuropathy are absent. Urinary and plasma porphyrin levels are normalized (Fig. 1c and d).

Discussion

The liver has been shown to be the organ causing metabolic alterations and clinical symptoms both in previous reports on liver transplantation in AIP [7,8] and in this report. The regression of neuropathic manifestations after liver transplantation suggests that the neuronal disease is driven by processes in the liver and argues against a clinical importance of extra-hepatic PBGD-deficiency. Porphyrogenic drugs [14] such as nitrofurantoin did not provoke symptoms. Different immunosuppression schemes have been safely used after marrow or kidney transplantation in AIP (e.g. [9–11,15]). Two major concerns seem to have been resolved: AIP is truly a hepatic porphyria that can be cured by liver transplantation and the remaining PBGD deficiency in extra-hepatic tissues lacks clinical relevance after liver transplantation. The available clinical data argue against the need for a conservative approach in drug choices such as ours in choosing nebulized pentamidine for pneumocystis pneumonia prophylaxis.

To our knowledge, nine women have now been transplanted: four in England [7,8], three in Sweden (present report and case below), one in France (JC Deybach, Spanish Porphyria meeting, Madrid 2008) and one in Finland (R Kauppinen, Porphyrins and Porphyrias, Stockholm 2009). All patients had severe symptoms and secondary organ damage. The first liver transplant in AIP was performed in 1993 in a Swedish patient who developed liver failure after a hepatoma resection.

These nine cases illustrate the indications for and the timing of transplantation in AIP. Liver transplantation is the last resort when other therapies [12] have failed. In AIP, it may be particularly difficult to weigh the risks and benefits of liver transplantation. A major problem is that liver transplantation is not considered in the first place, before complicating or contraindicating factors arise. There is always the risk that the subsequent acute attack might result in severe, possibly irreversible consequences.

An extended period of frequent hospitalizations with a poor quality of life would seem to constitute a reasonable indication. However, the natural course of AIP is sometimes unpredictable and this complicates the discussion. For example, there are a few reports of amelioration of the disease after years of frequent attacks or after menopause [16,17].

Liver transplantation should be considered early before a combined liver–kidney transplant is required or the metabolic misery of end-stage renal disease jeopardizes this option. It is reasonable to argue that liver transplantation in acute porphyria should be limited to a few strict indications: patients with recurrent severe attacks and an anticipated risk for severe consequences and patients with secondary complications such as severe neurologic symptoms, chronic hypertension, progressive nephropathy or hepatocellular carcinoma.

The two cases presented in this report both had a clear indication for combined liver–kidney transplantation. Both had a very poor quality of life resulting from acute porphyria symptoms, frequent hospitalizations, chronic neuropathy and renal failure necessitating dialysis. They had no meaningful alternative to combined transplantation if subsequent life-threatening consequences were to be avoided.

The definitive cause of renal disease was never histologically determined in these cases. This did not interfere with the decision to transplant. Whether the renal impairment was mainly secondary to hypertension, interstitial tubular damage [6] or noxious effects on renal parenchyma caused by porphyrin precursors, porphyrins or frequent heme administration remains speculative.

A selective increase of PBG in urine and of PBG and porphyrins in plasma paralleled deteriorating renal function. This phenomenon has been reported previously [13] but the physiological mechanisms have not been clarified. Despite low ALA (data not shown), the metabolite regarded to be mainly responsible for neurotoxicity, neuropathy progressed. Unlike a previous report [18], dialysis did not improve the clinical course of AIP but may have

worsened neuropathy. After starting dialysis, the plasma porphyrin concentration rose further (Fig. 1b and d), which gave rise to skin lesions resembling porphyria cutanea tarda in case number two.

As seen in Fig. 1, the urinary excretion of PBG normalized within the first day after CLKT while the plasma porphyrins slowly returned to normal within a week, the latter possibly reflecting the rate of plasma-albumin turnover.

In conclusion, liver transplantation is now established as an important treatment option in severe AIP as it leads to a phenotypic cure, thereby improving both morbidity and mortality. Hopefully, future cases will be identified before the need for combined transplantation arises. In our experience, clinical evidence does not support a conservative approach in drug choice after liver transplantation despite the remaining extra-hepatic PBGD deficiency.

Authorship

SW: wrote paper. PH: analysed data and critically reviewed the text. ES, CA and DA: collected data and critically reviewed the text. BGE critically reviewed the text.

Conflicts of interest

None to declare.

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