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Case Report

Domino liver transplant from a donor with maple syrup urine disease into a recipient with phenylketonuria

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ABSTRACT

Classical phenylketonuria (PKU) presents a unique challenge for women of child-bearing age. In the context of pregnancy, poorly controlled hyperphenylalaninemia can result in a devastating constellation of outcomes for the baby referred to as the maternal PKU Syndrome. We present the case of a woman with classical PKU unable to maintain a restricted diet and refractory to pharmacological therapies. She elected to undergo a domino liver transplant, receiving an organ from a donor with classical branched chain ketoacid dehydrogenase deficiency (maple syrup urine disease). Plasma phenylalanine concentrations normalized within a few days after transplant and remained so on an unrestricted diet during the first year of follow-up. The patient reports subjective improvements in mood, energy level, and overall quality of life. In the appropriate clinical setting, liver transplant should be considered to provide metabolic stability for PKU patients, particularly women of childbearing age.

1. Introduction

Severe phenylalanine hydroxylase (PAH) deficiency causes classical phenylketonuria (PKU), a rare, autosomal recessive inborn error of metabolism. PAH converts the essential amino acid phenylalanine (Phe) to the conditionally essential amino acid tyrosine (Tyr). Deficient hepatic PAH activity results in systemic accumulation of Phe, which can cause severe neuropsychological impairment in the absence of sustained Phe-lowering therapy. [1] For more than 50 years, PKU has been identified by newborn screening and managed by dietary Phe restriction. As a result, patients must severely limit most common protein sources and consume specialized medical food to provide appropriate intake of other amino acids to support normal growth, development, and subsequent health.

Adherence to the specialized PKU diet is difficult, leading to a vast majority of adolescent and adult patients having plasma Phe concentration outside the therapeutic range as defined by the American College of Medical Genetics treatment guideline. [2,3] More recently, introduction of two FDA approved medications for the treatment of PKU have change the therapeutic landscape for this disease. Sapropterin reduces plasma Phe concentration in some patients, but few are relieved of dietary restrictions, and many are refractory. [4] In contrast, pegvaliase, an alternative enzyme therapy, can theoretically normalize plasma Phe concentration on an unrestricted diet in all PKU patients. However, side effects, cost, and non-response represent barriers to use. [5]

Although women affected by PKU retain fertility, pregnancy places additional stress on these individuals. The Maternal PKU Syndrome results from inadequate Phe management during pregnancy and is characterized by teratogenicity proportional to the degree of hyperphenylalaninemia. Devastating neurologic sequelae and congenital heart disease are common outcomes. [6]

Liver transplant provides a *phenotypic* cure for PKU. As ~95% of PAH activity resides in the liver, a successful liver transplant restores somatic PAH activity and plasma Phe level essentially to normal. [7] Originally

Abbreviations: PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; Trp, Tryptophan; Tyr, tyrosine.

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viewed as a drastic procedure for life threatening illness, improvements in patient survival and outcome have led to broadening of the indications for liver transplant. In the context of PKU, the availability of other therapies has not supported a need for liver transplant. However, in patients who fail or are unable to adhere to pharmacological intervention or dietary management, liver transplants represent an option. Here, we present the case of a woman with classical PKU who was unable to maintain a restricted diet and proved refractory to pharmacologic interventions. As a means to maintain metabolic control in advance of pregnancy, she was successfully transplanted with a domino liver graft from a donor with classical maple syrup urine disease (MSUD).

2. Case

A 27-year-old woman with classical PKU (compound heterozygous for *PAH* c.842C > T [p.P281L] and c.1315 + 1G > A) presented for evaluation for liver transplant. She had been diagnosed through newborn screening and was treated lifelong with dietary Phe restriction. Despite attempting a low-protein vegetarian diet, she had intermittent symptoms of headache and behavioral alterations with persistently elevated plasma Phe concentration well in excess of the therapeutic range (typically >1200 μmol/l; normal 30–120 μmol/l, therapeutic range < 360 μmol/l). Her disease had earlier been shown to be refractory to both sapropterin dihydrochloride and to pegvaliase, and both were no longer in use. She hoped to have children but feared the deleterious effects of uncontrolled PKU during pregnancy. After evaluation by a multidisciplinary team including transplant, genetics, neuropsychology, and her primary care team including her obstetricians, and extensive discussion of all potential alternatives, she consented to listing for liver transplant.

One year later, a potential donor liver became available from a 28-year-old female with MSUD (Homozygous for BCKDHA c1312T ≥ A [p.Tyr438Asn]). We have previously used livers from such patients with great success in domino procedures for transplant into patients with a variety of other genetic disorders with no evidence of branched chain amino acid metabolism imbalance in the recipients. [8–10] On admission, the patient's plasma Phe concentration was 1407 μmol/l. She underwent successful domino liver transplant. Intraoperatively, she had a partial hepatic artery thrombosis requiring revision of the arterial anastomosis with takedown of the common hepatic artery, thrombectomy and anastomosis of the donor right hepatic artery to the donor gastroduodenal artery. Use of an aortic conduit was specifically avoided and she initially underwent only partial closure of her abdominal fascia.

Her early post-operative course was notable for a mild acute cellular rejection treated with a bolus dose of methylprednisolone followed by rapid taper. She had a persistent right pleural effusion that briefly required a chest tube prior to resolution and developed cytomegalovirus viremia treated effectively with valganciclovir. About 7 months after transplant, with normal allograft function, she underwent abdominal wall reconstruction with full thickness musculocutaneous advancement and porcine-derived surgical mesh.

Initial post-transplant plasma Phe concentration normalized on post-operative day 2 and remained so thereafter. Table 1 shows results of undirected metabolomic analysis performed both pre-transplant and post-transplant. We observed a precipitous decrease of Phe metabolites and conjugates, and an increase in Tyr and tryptophan (Trp) metabolites. Critically, cysteine glutathione disulfide, a marker of increased oxidative stress recently recognized as a phenomenon in mice, pigs, and humans with PAH deficiency, was elevated prior to transplant and returned to normal after the procedure. [11] One-year post-transplant, plasma Phe concentrations remain normal with an unrestricted diet and with normal plasma branched chain amino acid concentrations (Table 2). Her mood disturbance and headaches have resolved, and she reports dramatic improvement in her quality of life. She has continued to do well at her semi-annual follow-up (POD 655) with normal liver function tests, single agent immunosuppression with tacrolimus, no need for antihypertensive medications, a calculated GFR > 90 ml/kg/min without evidence of proteinuria. She has not had recurrence of CMV viremia and does not have EBV viremia on whole blood PCR. Our patient is currently in the process of planning her family and will continue follow-up with a high-risk obstetrician/ gynecologist along with our transplant team.

Table 1
Comparison of pre- and post-transplant metabolomic data.

	Pre-Transplant	Post-transplant
Phe Analytes[#]		
Glutamylphenylalanine	+++++	+
acetylphenylalanine	++++	+
formylphenylalanine	++++	+
Phenylacetate	++++	nd
Phenyllactate	+++++++	+
Phenylpyruvate	+++++	nd
Tyr Analytes[*]		
Glutamyltyrosine	+++	++++
acetyltyrosine	+++	++
Gentisate	++++	+++
4-hydroxyphenyllactate	++++	++++
4-hydroxyphenylpyruvate	++++	++++
Trp Analytes[+]		
acetyltryptophan	++	+++
serotonin	+++	+++
indoleacetate	++	++
kynurenine	++	++++++
Glutathione pathway		
cysteinylglycine	+++	+
cysteine-glutathione disulfide	+++++	nd

Pretransplant quantitative Phe 1362 μM, posttransplant 76 μM;
* Pretransplant quantitative Tyr 49 μM, posttransplant 52 μM
+ Both pre- and posttransplant, Trp was <10 μM.
nd, non-detectable

3. Discussion

Standard of care PKU management has classically focused on dietary protein restriction with use of medical foods to provide other necessary amino acids to prevent overall protein deficiency. [1] However, in nearly all patients, plasma Phe concentrations increase with age on dietary therapy and most adolescents and adults have levels that exceed the recommended threshold of 360 μMol/l. [2,3] Even among well-controlled patients, residual psychomotor disease is common, and can include executive dysfunction, mood disorders, tremors, and a variety of other late-onset phenotypes (neuropsychiatric, Parkinsonism, seizures, etc.). [4] Progressive cognitive impairment with advancing age can occur in adults who do not adhere to a Phe-restricted diet. [4] A 2015 survey by the National PKU Alliance found that more than half of respondents found it "difficult" to remain on dietary therapy and 90% believed a new approach to therapy was important. [12] They cited reasons such as wanting greater protein intake, reduction in medical food use, improvement in mental health, and reducing serum Phe concentration. In this cohort, 62% of respondents had plasma Phe concentrations above the recommended therapeutic range. [12] Pharmacological PKU management included cofactor and enzyme substitution therapies have provided substantive change in management for many patients but come with their own logistical challenges and risks, and both strategies proved unsuccessful in our patient.

Women with classical PKU who are of childbearing age represent a uniquely vulnerable population. This group comprises between 3000 and 4000 individuals in the United States, with several hundred more women aging into this category each year. [13,14] The potential impact of the Maternal PKU Syndrome upon unplanned pregnancy is staggering, particularly in woman with a historic inability to maintain plasma Phe concentrations within the therapeutic range. Although medical and dietary services are generally accessible for many women

Table 2
Prompt and persistent normalization of phenylalanine metabolism without aberrations in branched chain amino acid levels four hours after reperfusion of a liver allograft from a patient with classical MSUD (branched-chain alpha-keto acid dehydrogenase complex deficiency). Note the 13-fold reduction in plasma phenylalanine on post-operative day one.

Days from transplant	Phenylalanine (μmol/l)	Tyrosine (μmol/l)	Phe/Tyr	Valine (μmol/l)	Leucine (μmol/l)	Isoleucine (μmol/l)
Normal	**30–120**	**20–130**		**140–370**	**30–220**	**30–100**
−358	1537	44	34.93	164	69	41
−1	1407	46	30.59	177	82	47
0	1375	49	28.06	158	68	39
1	108	67	1.61	193	136	85
11	76	52	1.46	209	92	79
375	74	–	–	–	–	–

with PKU in the United States, very few mothers initiate dietary restriction before pregnancy, indicating that simple economic factors are not the only ones at play. [13,15]

Pregnancy brings additional challenges to women with PKU. Phe is actively transported across the placenta, resulting in fetal concentrations 1.25–2.5 times that of maternal blood. [16] Thus, even marginally elevated maternal plasma Phe levels can expose the developing fetus to teratogenic concentrations. The result of intrauterine Phe exposure varies, but can include structural heart defects, microcephaly, low birth weight, neurocognitive deficits, and behavioral disturbances. [4,6,15] To further complicate the situation for these women, recommendations for metabolic control for expectant women, or those planning to conceive, are especially arduous, including bi-weekly blood Phe measurements and tight control to maintain plasma Phe within the therapeutic (i.e., non-teratogenic) range. Tight maternal control of Phe levels below 360 μmol/l, ideally before conception, has been shown to offer the best neurocognitive prognosis. [6,17] However, expectant mothers experience significant difficulty even maintaining a more relaxed goal of <600 μmol/l. [6,17] Neonatal microcephaly rates reached as high as 46% in babies of the women unable to maintain plasma Phe concentration in the therapeutic range. [18]

The combination of strict guidelines to optimize fetal outcomes, inability to maintain dietary therapy, and inadequate pharmacological alternatives led us to consider liver transplant in one young woman with PKU who presented to us with the desire to bear children. Despite several attempts in the past to maintain strict metabolic control, both with and without sapropterin dihydrochloride and pegvaliase, she felt that she would ultimately fail again, particularly with the increased rigor required to maintain control during pregnancy. Several lines of evidence support liver transplant as a viable treatment for patients with classical PKU. Similar to the history of liver transplant for MSUD, there is a single case report in the literature demonstrating biochemical cure of a child with PKU who was transplanted for unrelated cryptogenic cirrhosis. [7] PAH shows primarily hepatic expression (with minor expression in kidney). Thus, as compared to MSUD, PKU is even more amenable in principle to curative liver transplant. [19,20] Accordingly, plasma Phe concentrations rapidly normalized and have persisted in the normal range for the first post-transplant year and we expect liver transplant to be a sustained cure resulting in continued normalization of Phe metabolism resistant to the stress of pregnancy.

Liver transplant carries its own associated risk when considering pregnancy. The first successful pregnancy after liver transplantation was reported over forty years ago. [21] Since that time, numerous single center series, literature reviews and registries have published the international experiences of pregnancy following liver transplantation. Delaying pregnancy at least one year after transplant has been suggested to improve maternal and fetal outcomes, with higher rates of low birth weight, rejection and graft loss if conception occurs less than 6 months after transplant [22] Immunosuppressive regimens must consider the potential effects on the developing fetus. High doses of corticosteroids, such as those used to treat active rejection, cross the placenta and can affect the developing fetus. [22] Assuring a stable immunosuppressive regimen prior to transplant is critical. Tacrolimus-based regimens are generally preferred due to lower rates of pre-eclampsia compared to cyclosporine-based regimens and as mycophenolate is contraindicated in pregnancy, azathioprine has been used safely as an adjunct when necessary. [22] Overall, maternal and perinatal outcomes are favorable after liver transplantation despite a higher incidence of preeclampsia, need for Caesarian section and secondary preterm birth with associated secondary perinatal morbidity and mortality. [23] As all post-transplant pregnancies are classified as “high risk”, modern reviews have noted excellent maternal and pregnancy outcomes, even if complicated by hypertensive complications due to early diagnosis and management. [23–26] Pre-eclampsia is the most and potentially life-threatening pregnancy-associated hypertensive disorder and was found to complicate 7–12% of pregnancies after liver transplant compared to roughly 4% of the general population. Similarly, gestational diabetes occurred more commonly in post-liver transplant pregnancies (8.6%) compared to the non-transplanted population (5.4%). [22–26] Rejection, mortality and graft loss is a rare complication of pregnancy after liver transplantation often associated with withdrawal or changes in immunosuppression. [22–26] A single maternal death was reported in 2003 due to thrombosis of an infrarenal aortic graft and secondary hepatic necrosis. [27]

Neonatal outcomes from mothers who have undergone liver transplantation have been rewarding. Among various studies, the live birth rate (LBR) in pregnancies after liver transplant ranges from 65 to 84% with increased LBR over the time of the studies. These LBR are equivalent to the general population, with similar incidences of spontaneous abortions and stillbirths. Pre-term births are more common in transplant recipients, as is the incidence of intra-uterine growth restriction and birth by cesarean section. These findings are likely due to the increased obstetric complications, such as pre-eclampsia. Congenital malformations, often feared by prospective mothers who have undergone liver transplant have not been found to be higher in this group, when compared to the general population. [22–26] Careful monitoring by high-risk obstetricians, in consult with the transplant team are vital in these cases.

Our patient continues to thrive in her second year after transplant. Her immunosuppression has been successfully weaned without evidence of graft injury and will undergo surveillance allograft biopsy on her five-year anniversary. She has no hypertension or evidence of renal dysfunction. Although she has not yet reached her ten-year anniversary, her status meets the objective requirements of “Ideal Transplant Survivor” as described by the Society of Pediatric Liver Transplantation in 2012. [28]

In this case, we utilized a liver allograft from a domino donor with MSUD, which has been well-studied as a safe option for domino donation without risk of causing iatrogenic MSUD in the graft recipient. [8–10] Since only 10% of total body branched chain ketoacid dehydrogenase is localized to liver, [19] the use of obligate carrier donors for MSUD as living donors for patients has been controversial. However, the high expression of the *PAH* gene in liver along with the relatively spared expression of heterozygotes leaves little concern for carrier parents with one defective *PAH* gene to voluntarily serve as a living donor to a child with classical PKU. Though there is some evidence to suggest

extrahepatic expression of PAH, [20,29] the level is likely too low to allow an explanted PAH-deficient liver to be used as a domino donor liver, as the recipient is likely to exhibit nearly the same level of PAH deficiency as donor. Utilization of a liver from a donor with PKU has not been reported but could be considered in certain clinical settings in which the risk of PAH deficiency would be outweighed by the condition of the potential candidate.

There are obviously other potential reproductive mechanisms for women with poorly controlled PKU to consider. Surrogacy following egg harvest and in vitro fertilization removes the risk of maternal PKU syndrome, but has its own cultural, religious, and ethical considerations. Hepatocyte transplant and gene therapy are both currently in clinical trials but currently exclude pregnant women, and the likely time to, and the uncertainly of approval were significant barriers to further consideration by the patient and her husband. In the end, both considered the risks of a liver transplant to be far outweighed by the benefits of normal Phe metabolism.

4. Conclusions

In summary, the course of this patient confirms that liver transplant can be successfully used to treat PKU with resulting normalization of plasma Phe concentration. Liver transplant offers an option to achieve metabolic stability to support the health of both the mother and developing fetus for PKU-affected women of child-bearing age unable to maintain metabolic control with standard of care. Use of living donors or potential use of domino allografts from patients undergoing elective liver transplant for Maple Syrup Urine Disease offers the potential for liver transplantation for well selected patients with PKU without the loss of a traditional donor allograft liver from the population.

Declaration of Competing Interest

The authors of this manuscript have no conflicts of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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