Liver Transplantation for Acute Intermittent Porphyria

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Key points

- Occurrence of acute intermittent porphyria
- Neurovisceral symptoms
- Pathophysiology of AIP
- Potential therapies for acute intermittent porphyria
- Recurrent symptoms after biochemical normalization with givosiran
- Liver Transplantation complications - renal and neurological impairment
- Pre-transplant morbidity
- Patient mortality rate

Heme, a crucial part of haemoglobin, is formed from porphyrins. Every haemoglobin sub-unit is a globular protein with an embedded heme group, which has one iron atom and can bind one oxygen molecule. Every step of the multi-step heme production route requires a different enzyme. Porphyrias are hence unique clinical syndromes that result from a lack of or a flaw in a single enzyme required for a particular step of the heme production pathway. Depending on which enzyme is defective and the accompanying heme precursor or porphyrin buildup, the clinical presentation, severity, and prognosis of each individual porphyria will vary. The most prevalent and severe type of acute porphyria is known as acute intermittent porphyria (AIP). Porphobilinogen-deaminase, commonly known as hydroxymethylbilane synthase (HMBS), is the third enzyme in heme production and is the main enzyme involved in AIP. The unregulated over-expression of the ALA synthase enzyme causes the acute attacks of AIP.1 Hence acute intermittent porphyria is an autosomal-dominant hepatic condition brought on by hydroxymethylbilane (HMB) synthase's sub-optimal activity.2

Neurovisceral symptoms

The putative neurotoxic porphyrin precursors which are 5-aminolevulinic acid (ALA) and porphobilinogen are markedly accumulated in symptomatic individuals during life- threatening acute neurovisceral attacks that are triggered by factors that cause the hepatic expression of 5-aminolevulinic acid synthase 1 (ALAS1) (PBG).3 Abdominal discomfort is followed by mental symptoms and then peripheral neuropathies in order of severity. The pain in the abdomen is often colicky, intense, and epigastric. It typically lasts several days. Constipation and vomiting may accompany it. Patients may exhibit a wide range of psychological symptoms, such as depression, along with concomitant neurologic and/or gastrointestinal symptoms. According to a Swedish study, both patients with AIP and their family had an elevated chance of schizophrenia or bipolar disorder. Although any nerve distribution may be impacted, peripheral neuropathies might present as a weakness that starts in the lower extremities and progresses upward. This symptomatology may resemble Guillain-Barre syndrome (GBS). Secondary to autonomic neuropathies, hypertension and tachycardia can also happen. Delirium, paralysis that progresses to quadriplegia and respiratory failure, cortical blindness, and even coma are examples of central nervous system symptoms.

Patients may experience seizures in 5% of instances, with partial seizures being the most frequent sub-type. Urine that is occasionally red or brown may be seen; this urine darkens when exposed to air, light, and heat. It's vital to note that AIP lacks any cutaneous symptoms, in contrast to porphyria cutanea tarda. In a recent case-control research (2017) involving 50 patients, it was discovered that acute intermittent porphyria and systemic inflammation are related. According to Storjord et al., only symptomatic individuals had lower levels of insulin, C-peptide, prealbumin, and kidney function indicators than asymptomatic patients. They hypothesized that decreased insulin release is linked to increased disease activity and deteriorated renal function in AIP in symptomatic patients.1

Pathophysiology of AIP

Women are more likely to experience acute bouts of acute intermittent porphyria, particularly in the post-pubertal age range. The acute bouts of AIP are often brought on by a number of things, such as alcohol, fasting, certain medicines, infections, and steroid hormones. Due to the buildup of porphyrin precursors, porphobilinogen, and aminolevulinic acid in acute intermittent porphyria, there is brain impairment (ALA). The neurological damage caused

by AIP presents as psychiatric symptoms as well as peripheral and autonomic neuropathies. Since the majority of people with the genetic mutation do not exhibit symptoms while having an excessive amount of porphyrin secretion, the precise mechanism by which elevated amounts of porphobilinogen and ALA induce clinical sickness is still unknown.1

Potential Therapies for Acute Intermittent Porphyria

Enzyme Replacement Therapy (ERT) - The European Medicines Agency (EMA) granted recombinant human HMBS/PBGD an orphan designation (EU/3/ 02/103) in 2002 based on the results of administering doses of recombinant human HMBS/PBGD (rhPBGD) protein in a mouse model of AIP that reduced plasma PBG accumulation during an acute attack induced after phenobarbital challenge. Clinical experiments were performed in healthy volunteers, asymptomatic HMBS-deficient individuals with elevated porphyrin precursor excretion, and AIP patients who experienced recurrent attacks. Despite the enzyme's ability to detoxify PBG metabolites, there were some drawbacks to the therapeutic approach, including the liver's lack of liver targeting and the enzyme's brief half-life in circulation.

Liver Gene Therapy - In clinical trials for patients with AIP, interfering RNA for ALAS1 gene inhibition and HMBS-gene therapy are being used. The HMBS gene is delivered to the hepatocytes via a viral vector as one of the two ways. The alternative is to use a small interfering RNA (siRNA) that is intended to inhibit aminolevulinic acid synthase in order to lessen the formation of delta ALA. Due to larger trials that should ideally show consistent efficacy and safety, both of them are still in the trial stage and awaiting approval.1

Recurrent symptoms after biochemical normalization with Givosiran

Givosiran, a siRNA that specifically down-regulates ALAS-1 expression in hepatocytes, was given approval by both the European Medicines Agency and the US Food and Drug Administration in 2019 to treat acute porphyric attacks. Givosiran has demonstrated encouraging results in lowering urinary levels of porphobilinogen (PBG) and 5-aminolevulinic acid (ALA), as well as in reducing the frequency of acute porphyric attacks.4

CASE SUMMARY

After givosiran achieved biochemical normalization of her urinary 5-aminolevulinic acid (ALA), porphobilinogen (PBG), and total porphyrins, a 47-year-old woman with acute intermittent porphyria (AIP) experienced recurrent symptoms. She has maintained normal urinary ALA, PBG, and porphyrin levels throughout treatment with no rebound in her laboratory test results. She has also had modestly impaired renal function and normal liver testing. Her monthly givosiran injections are being tolerated with no side effects, but every 1-2 months, she still has what she perceives to be acute porphyric attacks. She reported abdominal pain, generalized, stabbing neuropathy in her upper and lower extremities, fatigue, nausea, and vomiting, as well as photosensitivity in sun-exposed areas. She experienced acute AIP exacerbations almost monthly, usually after ovulation during the luteal phase of her menstrual cycles. She claimed that after the first few days of the monthly givosiran injections, her symptoms only slightly worsened, but she continued to experience postprandial and chronic stomach discomfort, peripheral neuropathy, muscle aches, brain fog, exhaustion, sad mood, and sleeplessness. AIP bouts necessitated numerous additional hospital stays, but she continued to reject Intravenous heme because of a prior consequence of pulmonary emboli. She was unable to eat throughout those stays because of excruciating postprandial sickness. She still experiences what she believes to be typical acute porphyric attacks every 4-6 months, but she has experienced less acute attacks because to continuous monthly givosiran and treatment from the chronic pain expert.4

Liver Transplantation

Recurring attacks are frequently challenging to manage and may cause chronic symptoms, especially persistent neuropathic pain and progressive neuropathy that significantly lower quality of life.2 Regular heme infusions have been used to treat AIP with recurrent attacks, and it has been reported that patients get better after years of treatment. However, waiting too long for spontaneous improvement before considering LT increases the risk of complications like renal impairment, iron buildup, progressive neurological impairment, and worse outcomes after LT.3 AIP patients in Europe who had failed medical treatment for their repeated severe attacks underwent orthotopic liver transplantation (OLT) recently. Up to 10 years following transplantation, patients who had successful transplants saw their urine ALA and PBG levels return to normal. However, Acute porphyric attacks with elevated urine ALA and PBG levels were observed in recipients of "domino" liver transplants made from the explanted livers of AIP patients into nonporphyric recipients with hepatocellular cancer.2

Pre-Transplant Morbidity

Neuropathy (68%) and renal impairment (51%) were the most prevalent comorbidities. Several people experienced secondary hemochromatosis (20%) or central venous thrombosis (20%) as a result of their heme therapy. The other reported concomitant illnesses included arterial hypertension, opioid use, recurrent infections, depression, and anxiety.3

Neurological Impairment

After LT, the majority of patients saw improvements, with no

neurological deterioration progression. There were fewer patients with paresis or decreased motor function, mobility, or neuropathic discomfort. A higher likelihood of residual neuropathy after LT was associated with severe motor neuropathy at LT, frequently in conjunction with a younger age at the onset of symptomatic AIP.3

Renal Impairment

Many deaths, soon after LT and afterwards were associated with renal impairment. Very few statistics on renal damage after LT for AIP have been recorded.3

Transplantation Complications

In 39% of transplant recipients, no side effects noted. In 26% of the patients who had transplants, there were minor problems including acute rejection, CMV viremia, various infections, cholangitis, and deep venous thrombosis. Severe issues such as bile duct obstruction or leakage, tissue rupturing from wounds, human herpes virus-6 infection leading to multiorgan failure, and late bleeding necessitating surgical intervention, were noted in 35% of cases.3

Patient Mortality Rate

For patients with AIP (n = 38), patients who underwent transplantation for other metabolic disorders (n = 2941), and all patients who underwent transplantation throughout the ELTR partnership (n = 98,376) from 2002 to 2019, a Kaplan-Meier curve plot of overall patient survival was created.3

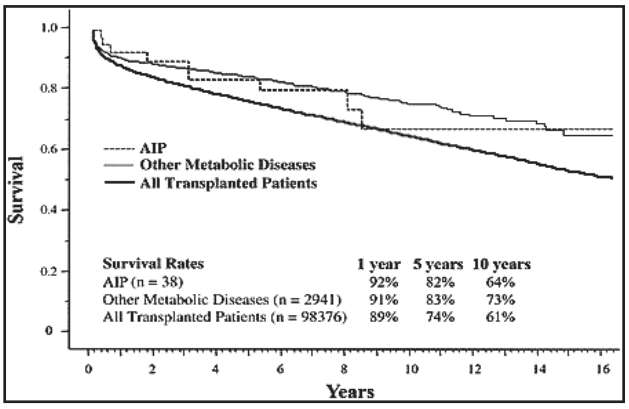

Figure 1: Patient mortality rate3

Conclusion

This study demonstrates that LT provides a good chance of curing AIP symptoms. The neuropathy caused by porphyria improves, although the risk of unfavorable results is increased by severe neuropathy and significant renal impairment prior to transplant. A transplant center should be involved in the discussion at an early stage, before AIP-related comorbidity is complex or severe, and patients with AIP who have recurrent attacks, signs of renal impairment, and/or severe neuropathy and do not respond to other therapeutic options should be considered for LT.3

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