Liver transplantation for intermittent acute porphyria resistant to medical treatment☆

Trasplante hepático por porfiria aguda intermitente resistente a tratamiento médico

Acute intermittent porphyria (AIP) is a rare metabolic disease. Patients are usually either asymptomatic or able to control their symptoms by avoiding triggers and administering intravenous hemin during neurovisceral crises[1,2]. A small number of patients have attacks that are resistant to treatment, resulting in a very poor quality of life[1,2]. In 2004, the first liver transplantation used as treatment for AIP was published[2]. We have conducted a systematic review of the literature in PubMed using the search terms "liver transplantation and acute intermittent porphyria", which identified 41 articles; 9 of these studies included a total of 17 patients who underwent transplantation for AIP (Table 1)[1]. We present a patient affected by AIP who did not respond to conventional treatment and was therefore treated with liver transplantation (LT).

The patients is a 42-year-old woman who began experiencing symptoms of severe abdominal pain, dark urine and hyponatremia in 2011. Hoesch test was positive, with elevated urinary porphobilinogen (PBG) (54.4 mg/24 h) and 5-aminolevulinic acid (ALA) (172 μmol/24 h) levels. The genetic study revealed mutations 669–698 of 30 in the gene encoding for the PBG-deaminase enzyme. With a diagnosis of AIP, treatment was initiated with intravenous hemin when the patient had crises, which initially achieved clinical improvement.

The patient continued to have increasingly frequent attacks triggered by stress or menstruation, which required monthly prophylactic hemin. We tried genetic therapies (included in the DIGNA-2011 study with the rAAV2/5-PBGD genetic vector) and prophylactic oophorectomy, but these were not effective. The patient's condition became more complicated, leading to osteoporosis, weekly neurovisceral crises that were difficult to control with hemin and analgesia, CNS symptoms (visual hallucinations, agitation, delirium) and a progressive increase in opiate use, leading to secondary addiction. The decision was made to add her to the LT waiting list. In March 2019, she received an organ from a brain-dead donor (donor risk index: 2.5). Induction was begun with basiliximab, mycophenolate mofetil and corticosteroids. Tacrolimus was introduced on the 4th day post-transplantation. Urine porphyrins became negative on day 2 after transplantation. The ICU stay was 10 h, and the patient was discharged from hospital on the 6th day. In the explant, a large amount of iron was observed in the hepatocytes, a consequence of treatment with hemin (Fig. 1). After 15 months of follow-up, PBG and ALA levels are normal, and the patient has presented no exacerbations, nor has she required analgesic treatment.

AIP is the most common acute porphyria and belongs to the group of hepatic porphyrias[1–5]. It is an autosomal dominant transmission disease caused by partial porphobilinogen deaminase deficiency, which causes an accumulation of ALA and PBG[1–5]; it is more frequent in women[1].

Some 90% of patients are asymptomatic[2]. Symptomatic patients present neurovisceral abdominal pain crises, without skin photosensitivity, triggered by factors that increase the demand of the heme group (stress, drugs, alcohol, eating, hormonal changes, etc)[1,2,4,6]. Other symptoms that can accompany crises include: vomiting, constipation, urinary retention, tachycardia, blood pressure alterations, motor neuropathy and convulsions[1–3]. The diagnosis is based on increased urinary levels of ALA and PBG[5].

Treatment involves avoiding triggers of the attacks (by suppressing ovulation), analgesia, hydration, and a diet rich in carbohydrates, while intravenous hemin is administered during attacks[1,2,4,6]. 90% of patients with porphyria progress satisfactorily with these measures, but a small group of patients continue to present frequent crises[1,2]. In addition, chronic treatment with hemin causes several complications, such as liver fibrosis due to iron storage and/or progressive resistance to treatment[1,2,6–8]. Recurrent symptoms and multiple hospital admissions cause these patients to have a poor quality of life and a lower life expectancy[1,2].

The pathogenesis of the attacks is unknown, although it is believed that they occur due to the hepatic production of porphyrin precursors as a result of the underlying metabolic deficiency[2,6]. Therefore, LT is the only curative treatment since the deficient enzyme is replaced[1,2,4]. The most widely accepted indications for LT in AIP are crises that do not respond to treatment with hemin, poor quality of life, progressive neurological disease, or liver failure due to hemin overdose[1,4,5]. The results obtained with LT in AIP are difficult to interpret due to the small number of published cases (Table 1)[1,6,9–11]. There is only one series of 10 transplant patients with AIP belonging to the British registry, in which the indication for LT was poor quality of life, either due to

☆ Please cite this article as: Alcázar López C, Rodríguez Laiz GP, Sánchez Martínez R, Pascual Bartolome S, Ramia JM. Trasplante hepático por porfiria aguda intermitente resistente a tratamiento médico. Cir Esp. 2020. https://doi.org/10.1016/j.ciresp.2020.08.007

Table 1 – Cases published of AIP treated with liver transplantation.

Author/ year	N	Age	Sex	Time of symptoms (yrs)	Symptoms	Indication OLT	Type of transplant	Immediate post-OLT complications	Biochemical Normalization	Post-OLT porphyria attacks	Follow-up (months)	Retrasplantation	Death
Wahlin et al./ 2010[11]	2	24	Female	NE	Abdominal pain, Neuropathy, Kidney failure	Medically uncontrollable AIP symptoms	OLT + kidney transplant	No	Yes	No	16	No	No
		55	Female	10	Neuropathy, kidney failure	Medically uncontrollable AIP symptoms	OLT + kidney transplant	Biliary leak Rejected kidney	Yes	No	11	No	No
Dowman et al., 2012[6]	10*	31	9/10 Female	NS	Abdominal pain, Labile HTN and Neuropathy	Medically uncontrollable AIP symptoms	OLT	4 HAT 1 Biliary leak	Yes (10/10)	No (10/10)	23.4	1/10 due to HAT (13 days post-OLT)	2/10 (98 days and 26 months post-OLT)
Frei et al., 2012[4]	1	58	Female	35	Renal insufficiency and hypertension	Liver failure Hemin overdose	OLT	No	Yes	No	12	No	No
Yasuda et al., 2015[3]	1	36	Female	11	Neuropathy	Medically uncontrollable AIP symptoms	OLT	No	Yes	No	24	No	No
Malinzak et al., 2018[1]	1	30	Female	14	Abdominal pain, Neuropathy	Medically uncontrollable AIP symptoms	SPLIT Right liver	Kidney failure Collection	Yes	No	15	No	No
Spiritos et al., 2019[10]	1	16	Female	NE	Abdominal pain	Medically uncontrollable AIP symptoms	SPLIT Right liver	No	Yes	No	12	No	No
Al Samkari et al., 2019[9]	1	59	Female	18	Abdominal pain	Medically uncontrollable AIP symptoms	Living donor	NS	4 years post-LT, the door had unknown AIP	4 years post-LT, the door had unknown AIP	48	No	No
H. G. Alicante	1	42	Female	8.5	Abdominal pain CNS symptoms	Medically uncontrollable AIP symptoms	OLT	No	Yes	No	15	No	No
Total Series	18	35	Female 17/18	16	Pain abdominal (15:/18:84%)	AIP symptoms(17) Hepatic failure (1)	15 OLT 2 SPLIT, 1 Living donor	6/18 (33%)	No 17/18 (94.5%)	No 17/18 (94.5%)	21.5	1/18 (5.5%)	2/18 (11%)

NS: not specified; HTN: hypertension; HAT: hepatic artery thrombosis; OLT: orthotopic liver transplant.

* This publication includes cases by Soonowalla et al. and Dar et al.

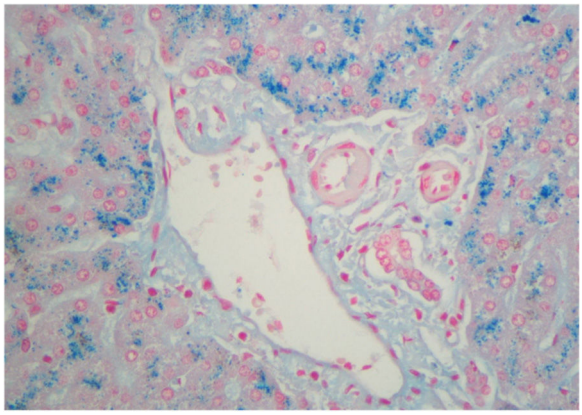

Fig. 1 – Liver biopsy: large quantity of iron accumulated in the hepatocytes as a result of treatment with hemin (Perl's Prussian blue). The color of the figure can only be seen in the electronic version of the article.

The median follow-up was 23.4 months, with two deaths 98 days and 26 months after surgery. A much higher rate than usual of arterial thrombosis was observed (4 cases)[6], and one of these 4 patients required retransplantation. The authors were not able to find an etiological explanation for the correlation between AIP and the high rate of thrombosis, but this may make it advisable to administer antithrombotic prophylaxis. PBG and ALA levels always normalized within 72 h post-LT, with no recurrence of abdominal crises, although neurological deficits were not recovered. 70% of the explants presented hemosiderosis, as in our case[6].

There are no reported cases of AIP recurrence after cadaveric LT. One recurrence has been published in a recipient who received a living donor transplant from a brother who had asymptomatic AIP[9]. In our case, all available treatments were tried, with no improvement, and the patient was resistant to treatment with hemin. We decided to perform LT as a last option, with excellent clinical results. As in most benign diseases susceptible to LT, determining the optimal time for transplantation is always difficult, but one should never wait for the onset of severe neurological symptoms due to the high risk of their not improving after LT[6].

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http://dx.doi.org/10.1016/j.cireng.2021.09.002