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Symptomatic Val122del mutated hereditary transthyretin amyloidosis: Need for early diagnosis and prioritization for heart and liver transplantation

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ABSTRACT

Background Hereditary transthyretin (ATTRv) amyloidosis is an autosomal dominant disease linked to transthyretin gene mutations which cause instability of the transthyretin tetramer. After dissociation and misfolding they reassemble as insoluble fibrils (i.e. amyloid). Apart from the common Val30Met mutation there is a very heterogeneous group of non-Val30Met mutations. In some cases, the clinical picture is dominated by a rapidly evolving restrictive and hypertrophic cardiomyopathy.

Methods A case series of four liver recipients with the highly clinically relevant, rare and particularly aggressive Val122del mutation is presented. Medical and surgical therapeutic options, waiting list policy for ATTRv-amyloidosis, including the need for heart transplantation, and status of heart-liver transplantation are discussed.

Results Three patients needed a staged (1 patient) or simultaneous (2 patients) heart-liver transplant due to rapidly progressing cardiac failure and/or neurologic disability. Domino liver transplantation was impossible in two due to fibrotic hepatic transformation caused by cardiomyopathy. After a follow-up ranging from 3.5 to 9.5 years, cardiac (allograft) function was maintained in all patients, but neuropathy progressed in three patients, one of whom died after 80 months.

Conclusions This is the first report in (liver) transplant literature about the rare Val122del ATTRv mutation. Due to its aggressiveness, symptomatic patients should be prioritized on the liver and, in cases with cardiomyopathy, heart waiting lists in order to avoid the irreversible neurological and cardiac damage that leads to a rapid lethal outcome.

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Introduction

Hereditary transthyretin (ATTRv) amyloidosis is an autosomal-dominant disease associated with transthyretin (TTR) gene mutations [1,2]. The disease has been divided into cardiac, neuropathic and mixed phenotypes depending on mutation, though large variations of phenotypes are found [2–5]. The instability of mutant TTR, mainly produced by the liver, facilitates disassembly into monomers that after misfolding and reassembling into insoluble extracellular fibrils, i.e. amyloid. Amyloid is deposited in most of the body's organs, but symptoms are most commonly derived from depositions in the heart, nervous system, gastrointestinal tract, eyes and kidneys [3,6,7]. The most prevalent mutation causing neuropathy, Val30Met, is endemic in Portugal, Sweden and Japan and predominantly presents as a progressive autosomal dominant distal sensorimotor polyneuropathy (DSPN) with variable systemic involvement [1,3,7,8]. The phenotypes of the non-Val30Met mutations vary, and some are also characterized by central nervous system symptoms. If left untreated, ATTRv-amyloidosis has an irreversible and fatal course within 7 to 12 years of onset [3,6]. Until the recent introduction of RNAi and antisense anti-amyloid treatment, liver transplantation (LT) has been the reference treatment to halt (or cure) this disabling and fatal hereditary neuropathy. Liver replacement stops the production of the mutant amyloidogenic TTR thereby treating the sensorimotor and autonomic neuropathy and accompanying organ involvements [2,4,6–9].

In cases of delayed diagnosis, which are frequent due to the usually insidious onset of the disease and the lack of a positive family history in 50% of late-onset cases, urgent combined or sequential heart-liver transplantation (CHLT) or isolated heart transplantation are the only therapeutic options for patients presenting with severe cardiomyopathy [2,7,10].

A case series of four ATTRv-amyloidosis patients (three requiring a CHLT) with the very rare and aggressive Val122del mutation is reported here for the first time in literature. In this context, a short review of CHLT in the therapeutic ATTRv-algorithm is also presented.

Methods

Data collected by the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR), located at Karolinska University Hospital in Stockholm, Sweden in relation to the different ATTRv mutations, incidence of domino LT (DLT) and CHLT were analyzed [2,10,11]. Just four cases of the Val122del mutation were reported to the registry by the Mayo Clinic, Rochester (Minnesota, USA) (1 patient), the Bellvitge University Hospital, Barcelona (Spain) (1 patient) and the University Hospitals Saint-Luc, Brussels (Belgium) (2 patients). The clinical course of these four patients, all of whom had a Hispanic origin, is presented here in detail. A short review of the literature in relation to CHLT is also presented.

The study was approved by the respective institutional review board and performed in accordance with the 2000 *Declaration of Helsinki* and the 2008 *Declaration of Istanbul*.

Results

Patient 1 (Barcelona)

A 62-year-old Spanish woman underwent a heart transplantation in March 2011 for heart failure due to restrictive cardiomyopathy. The patient had a 9-month history of progressive dyspnea and was in NYHA functional class III at the time of evaluation. Pre-transplant echocardiography showed a moderate left ventricular hypertrophy, left ventricular ejection fraction of 43% and a mean pulmonary arterial pressure of 62 mmHg. Endomyocardial biopsy confirmed the diagnosis of ATTRv- amyloidosis. Neurologic work-up indicated a grade I polyneuropathy disability (PND) score. She was already known to have a Val122del mutation in the TTR gene in heterozygosis that had been diagnosed after bilateral carpal tunnel operation 15 years ago. Anamnesis revealed a grandmother with heart disease. Six family members with the same mutation were evaluated; four are presently asymptomatic and two are treated with tafamidis (Vyndaqel® Pfizer, USA) for symptomatic cardiomyopathy. Five months later she underwent an LT. The pre-LT evaluation revealed normal liver morphology, elastography and function. At day 10 a bile leak required a hepaticojejunostomy. Immunosuppression (IS) consisted of quadruple drug therapy: anti-IL-2 receptor blocker basiliximab (Simulect®, Novartis, Switzerland), tacrolimus (TAC), mycophenolate mofetil (MMF) (Myfortic®, Novartis, Switzerland) and steroids. During the entire post-transplantation follow-up, her liver function remained very satisfactory with no rejection and liver tests remained normal. IS was adapted to her deteriorating renal function (GFR 45 mL/min/1.73 m^2) and frequent episodes of diarrhea. Maintenance IS consisted of slow-release TAC (Advagraf®, Astellas, Japan), low-dose mycophenolic acid and steroids. Five months post-LT the neurological disease worsened. After 9.5 years, she had a grade III PND and severe autonomous bladder and gastrointestinal dysfunction. She received treatment with diflunisal (Dolocid®, Merck Sharp Dohme, USA) from July 2016 to August 2018; this medication had to be stopped because of deteriorating renal failure and edema. The heart showed moderate left ventricular hypertrophy with normal left ventricular ejection fraction and no graft vasculopathy or cellular rejection at last follow-up. There were no signs of cardiac amyloidosis on ^{99m}Tc-DPD scintigraphy in 2017 and no amyloid deposition on the endomyocardial biopsy in 2018. Her liver was transplanted into a 66-year-old man suffering from end-stage HCV cirrhosis; he died 16 months later of disease recurrence.

Patient 2 (Mayo clinic)

A 62-year-old male of Hispanic origin underwent a CHLT in July 2012 for restrictive cardiomyopathy. His disease history started four years before with shortness of breath hindering from exercising. After evaluation in May 2010, he was listed for transplantation. Ejection fraction was 20% and he had a mild peripheral sensory (right hand paraesthesia) and autonomic neuropathy (grade I PND). He had no gastrointestinal symptoms. His heart condition worsened whilst his neurologic symptoms remained quite stable. In February 2012, he was re-hospitalized due to his cardiac condition which necessitated continuous inotropic in-hospital support until date of CHLT. This procedure was done under triple induction IS: anti-lymphocytic serum (Thymoglobulin®, Sanofi Genzyme, USA), TAC and MMF. The liver could not be used for domino liver transplantation (DLT) due to the presence of advanced fibrotic and congestive changes ("cardiac liver"). The postoperative evolution was favorable; 7.5 years later both allografts function normally under double IS using sirolimus and MMF. His neuropathy however progressed; he is still walking for one hour per day but has some muscle weakness resulting in difficulty in climbing stairs; he is on diflunisal treatment because of pain and sensory loss in a stocking distribution of both lower extremities (grade II PND). He has no gastrointestinal symptoms, nor other autonomic dysfunctions. He is being treated for prostatic cancer.

Patient 3 (Brussels)

A 59-year-old male was from a Spanish family with a significant history of ATTRv-amyloidosis. His father died at the age of

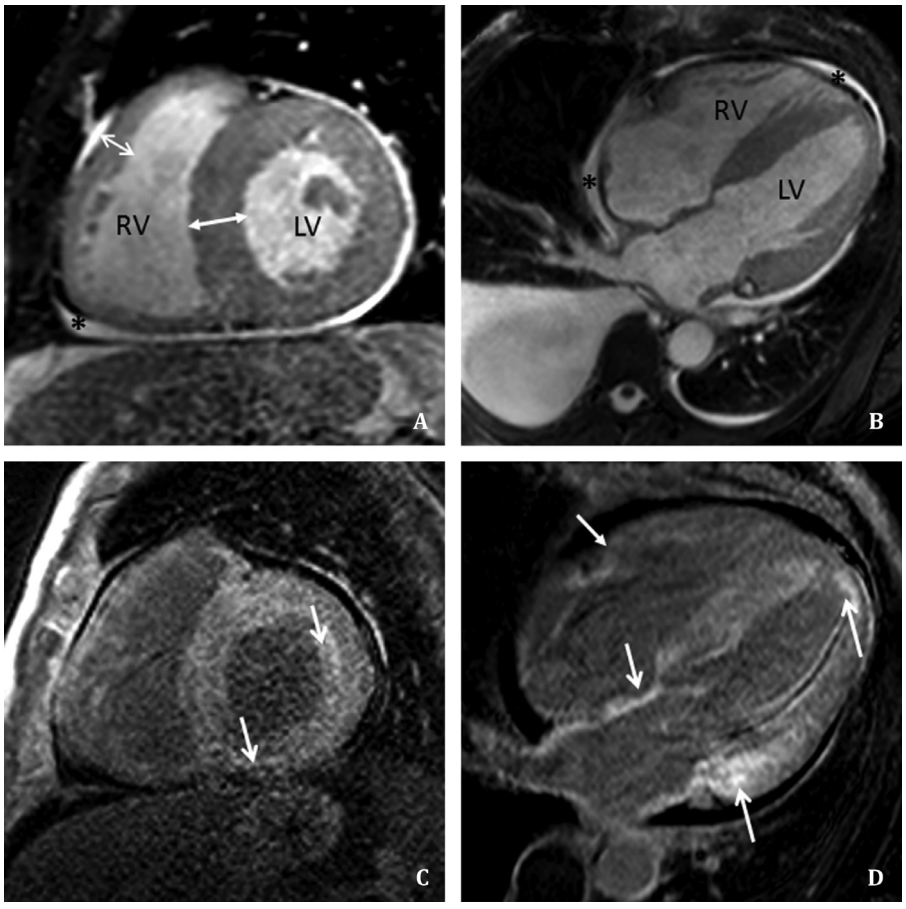

Fig. 1. Cardiac MRI (Patient 4). **A** and **B:** Diffuse hypertrophy of the myocardium on cine-SSFP images in short-axis (**A**) and four-chamber (**B**) views. The myocardium of the left ventricle (LV) and the right ventricle (RV) are severely thickened (arrows) and there is a mild pericardial effusion (*) as well as a bilateral pleural effusion. The interventricular septum measures 20 mm (normal < 11 mm). Cine-images demonstrated severe left ventricular systolic dysfunction (LVEF 33%) with diffuse hypokinesis. **C** and **D:** Late gadolinium enhancement (LGE) images in short-axis (**C**) and four-chamber views (**D**) after contrast medium administration. Diffuse, primarily subendocardial hyper-enhancement is seen in both the left and right ventricles as well as in the interatrial septum. The correct inversion time to eliminate the signal of myocardium could never be obtained, a pattern which is very specific of cardiac amyloidosis.

61 of the disease; one older brother suffering from cardiac decompensation and advanced DSPN had a CHLT in a late disease stage (see Patient 4); one 58-year-old brother refused LT despite the fact that he required a pacemaker for an atrio-ventricular block and had paraesthesia of upper and lower limbs; his homozygous twin brother has no major cardiac complaints yet (left ventricular ejection fraction of 44% and mean systolic pulmonary artery pressure of 33 mmHg) but has sensory disturbances of the lower limbs treated with tafamidis and finally another brother died whilst waiting for a combined heart-liver-kidney transplantation. In the context of this family background, ATTRv-amyloidosis was diagnosed early when he presented with bi-ocular diplopia and fainting. Anamnesis revealed that he had already had mild peripheral neuropathy for seven years. In view of his family history LT was readily proposed but refused by the patient and delayed for two years. Pre-transplant investigations confirmed the lower limb paraesthesia, preserved left ventricular function and an atrial tachycardia in the presence of a progressive concentric, non-obstructive, hypertrophic cardiomyopathy on gadolinium magnetic resonance imaging (MRI). After another two years, he underwent an isolated LT. Unfortunately, he had to be re-transplanted five months later because of a refractory rejection and hepatic artery thrombosis. After a difficult recovery, he is doing well 3.4 years later; his cardiac function remains good. His PND score before and after LT remained at grade I. His liver was successfully transplanted into a 61-year-old man with a hepatocellular cancer.

Patient 4 (Brussels)

The clinical history of this 61-year-old physically and extremely fit Spaniard is described in detail as it illustrates very well both the aggressivity of this mutation and therefore the justification for prioritization on both heart and liver waiting lists. His medical history started in 2000 with some lower limb paraesthesia. His medical and surgical history revealed a left cystic kidney, cholecystectomy, surgery for anal fistula and carpal tunnel syndrome. Based on progressive limb pain and sensorimotor disturbances the diagnosis of "idiopathic" DSPN was put forward in 2009, despite his heavy familial amyloidotic burden. At that time, he was still practicing his favorite sports activity, mountain climbing. By the end of 2011, his condition rapidly deteriorated becoming unable to walk without crutches (grade IV PND) and presenting autonomic disturbances i.e. sexual and bladder emptying troubles, palpitations and orthostatic hypotension. He was treated with gabapentin, sertraline and clonazepam followed by the placement of a neurologic stimulator. The genetic analysis confirmed the Val122del mutation. Due to the very rapid progression of his disease, going from complete fitness to an incapacitating state within less than 24 months, the indication for LT was put forward in February 2012. Pre-LT investigations revealed abdominal ascites and pleural effusion in the presence of a normal liver morphology on ultrasonography. Cardiac gadolinium MRI showed thickened cardiac walls, reduced left ventricular ejection fraction (33%) and mild pericardial effusion due to

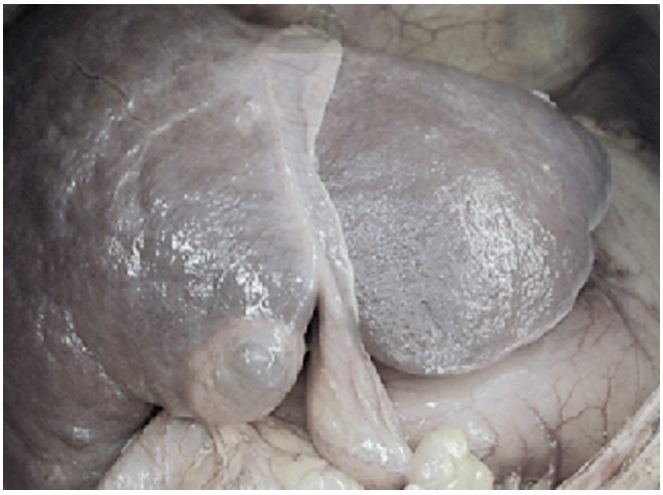

Fig. 2. Perioperative view of the fibrotic "cardiac" ATTRv liver at transplantation.

diffuse cardiac amyloid infiltration (Fig. 1). In June 2012, a complete atrio-ventricular-block required urgent pacemaker insertion. The cardiac decompensation was responsible for weight fluctuations of over 20 kg. Because of the rapid worsening of his cardiac status (NYHA functional class III at the time of evaluation), he was listed for CHLT. After several refusals by the Eurotransplant Cardiac Committee, he finally had, after much insisting by the liver team, priority status on both liver and heart waiting lists and was transplanted 8 months later. The heart was implanted first under cardiopulmonary bypass followed by a vena cava sparing LT without use of veno-venous bypass. DLT had to be canceled due to a severe liver fibrosis ("cardiac liver") (Fig. 2). IS consisted of rabbit anti-T-lymphocyte globulins (Grafalon®, Neovii Biotech GmbH, Germany), TAC, MMF and short-term steroids. He did not have any rejection episodes. The immediate and late postoperative course was complicated by an infected pleuro-pericardial effusion necessitating pericardial drainage and a severe herpes zoster infection. One-year routine follow-up revealed normal liver and heart functions, biopsies were normal, and showed no signs of amyloid deposition. His neurological condition initially improved significantly (grade III PND) but mild lower limb sensorimotor symptoms (pain and thermal sensibility) persisted and he required crutches to walk. Up until 64 months post-CHLT his neurological status remained similar. Both transplanted organ functions remained normal; renal function remained stable under TAC. From then onwards his general condition progressively deteriorated, and he died 80 months after transplantation due to his underlying disease.

Discussion

ATTRv-amyloidosis (formerly termed FAP) represents a large group of inherited autosomal-dominant neurological diseases due to many mutations of the TTR gene. Today, 146 different mutations have been reported (http://www.amyloidosismutations.com/mut-attr.php) [12]. The disease can also be caused by aging as seen in wild-type ATTRv-amyloidosis [2]. This senescence process explains the progression of symptoms after LT in some patients, especially in non-Val30Met mutations [2]. The knowledge of the exact type of mutation is of importance because of the variation in clinical disease manifestation, progression rate as well as outcome [2,3,7,8]. Outside high-penetrance areas, diagnosis can be difficult because ATTRv-amyloidosis may manifest at high age, without known family history and with atypical features [3]. Val30Met ATTRv-amyloidosis typically has an early-onset (between 25 and 35 years), a more benign course and a cardiac involvement in the form of brady-arrythmias. "Late-onset families" have been reported in this mutation [6,7,13–15]. Conversely, non-Val30Met ATTRv-amyloidosis typically has a late-onset presentation (> 50 years), a more rapid evolution with more functional impairment resulting in lower survival rates [6,7,14]. Most frequently patients develop an infiltrative, restrictive cardiomyopathy resulting in diastolic dysfunction and signs of fluid overload. Decreased systolic ventricular function appears late in the disease and is associated with terminal heart failure [3,7]. In general, the Val30Met mutation has a better prognosis compared to the other mutations in which cardiomyopathy dominates the clinical picture [2,3,6–8]. Apart from the type of mutation, nutritional status, severity of amyloidosis-linked complications, family history of the disease, age-at-onset and disease duration all influence outcome [2,3,6,7]. Early and late onset Val30Met patients have a different survival; non-Val30Met patients in contrast do not seem to have this discrepancy [16–18].

The care of ATTRv patients requires a multidisciplinary approach aiming at treating sensorimotor and autonomic dysfunctions, managing end-stage organ failure(s) and eventually halting amyloid formation [6,7]. Advances in medical treatment, better awareness and knowledge, all improved the follow-up of asymptomatic patients and allowed earlier treatment of symptomatic patients. Recently, stabilisers which prevent the dissociation of TTR into monomers, and gene silencers stopping (wild-type and mutant) TTR production have been introduced into clinical practice [6,7,19–25]. Diflunisal and tafamidis are nowadays the first-line anti-amyloid drugs; they are able to slow down or halt disease progression [4,21,22]. The TTR kinetic stabilizer tafamidis is currently indicated for the treatment of cardiac ATTRv-amyloidosis [4]. The gene silencing drugs, patisiran and inotersen are more effective as they inhibit the production of the mutated TTR protein, thereby following the same therapeutic principle as LT. It is expected that all these drugs will be of greater value in non-Val30Met patients [5,7,8,22–24].

The marked drop in LT reported to the FAPWTR, from around 120 to less than 25 yearly indicates that medical treatments have changed the therapeutic paradigm of ATTRv-amyloidosis, "reducing" the role of LT to symptomatic patients presenting with progressive neurological disease despite their medical treatment [11]. Although LT reduces the mutated TTR plasma concentration by 98% within a few days and stops the progression of the polyneuropathy in around 70% of patients, reversal of the disease has been seldom reported [2,3,6,7,11,26–28]. The first LT for ATTRv-amyloidosis has been done in 1990; until December 2019, 2266 LT have been reported to the FAPWTR [2,10,11,27]. DLT was done in 1223 (54%) patients and 80 (3.6%) patients had an HLT. The Val30Met mutation was the most frequent; 64 different non-Val30Met mutations were diagnosed in 290 (12.8%) recipients [2,3,7,10,11]. The FAPWTR data allowed to identify prognostic factors and improve timing of LT [2,10,11]. In non-responders to medical treatment, LT should be proposed for symptomatic patients and patients presenting with changes from baseline neurophysiological measurements due to biopsy proven amyloid deposition [7]. The correct timing of transplantation is important because outcome has been linked to pre-LT status. Once the "point of no return" is reached, clinical and/or functional recovery becomes unlikely despite the fact that LT can halt disease progression [6,7,21,23,28]. Post-transplant neurological improvement and 5-, 10- and 20-year survival rates are significantly better in Val30Met compared to non-Val30Met patients (79%, 69% and 55% vs. 64%, 42% and 14%, respectively) [2,3,6,7,11,17,28]. The markedly varying (10 years) survival rates (from 85% to 21%) in the non-Val30Met patients are explained by the mix of mutations which have different degrees of aggressivity, by the more rapid progression of the cardiac disease and of the polyneuropathy related to the more significant tissue deposition of wild-type TTR [2,7,13]. Progression of cardiomyopathy

Table 1
Combined heart-liver transplantation (CHLT): literature review including case series of 4 or more patients (listing following year of publication).

Studies	Study period	*n*	Indications	Patient survival			Comments and rejection rate
				1year	5-year	10-year	
Te et al. (2008) (UNOS registry) [31]	1987–2005	47	ATTRv ($n = 14$); HCV cirrhosis ($n = 6$); hemochromatosis ($n = 6$); cardiac cirrhosis ($n = 5$); cryptogenic cirrhosis ($n = 4$); alcoholic cirrhosis ($n = 3$); primary biliary ($n = 2$); A1-ATD cirrhosis ($n = 1$); primary sclerosing cholangitis ($n = 1$); Budd-Chiari syndrome ($n = 1$); autoimmune hepatitis ($n = 1$); lupus ($n = 1$); nodular regenerative hyperplasia ($n = 1$); glycogen storage disease ($n = 1$)	84.8%	75.6%	NR	Multicenter US cohort (15 centers); simultaneous kidney transplantation: 6 patients; tacrolimus monotherapy immunosuppression: 39 (28%) patients; cardiac rejection: 5 (10.9%) patients
Raichlin et al. (2009) (Mayo Rochester*) [13]	1992–2007	15	ATTRv ($n = 11$); cardiac cirrhosis ($n = 2$); hemochromatosis ($n = 1$); biliary cirrhosis ($n = 1$)	100%	83%	63%	Cardiac rejection: 2 (17%) patients; lower rejection rate compared to isolated HT 155/256 (60%) patients ($P < 0.02$)
Barreiros et al. (2010) (Univ. Mainz) [6]	1998–2007	4	ATTRv	75%	NR	75%	3 staged; 1 simultaneous *en-bloc* CHLT; DLT all patients
Rauchfuss et al. (2011) (Univ. Jena) [32]	2005–2010	4	Cardiomyopathy	75%			Cardiac rejection: 2 patients
Cannon et al. (2012) (UNOS registry) [33]	1987–2010	97	ATTRv ($n = 27$); cardiac cirrhosis ($n = 17$); hemochromatosis ($n = 6$); HCV cirrhosis ($n = 12$); cryptogenic cirrhosis ($n = 16$); alcoholic cirrhosis ($n = 4$); primary biliary cirrhosis ($n = 3$); primary sclerosing cholangitis ($n = 2$); metabolic disease ($n = 2$); acute liver failure ($n = 2$); cystic fibrosis ($n = 2$); carcinoid tumor ($n = 1$); Budd-Chiari syndrome ($n = 1$); biliary atresia ($n = 2$)	92.3%	79.9%	NR	Multicenter US cohort; cardiac rejection: 7 (8.9%) patients; lower rejection rate compared to isolated HT (23.9%) ($P = 0.002$)
Nelson et al. (2013) (Aarhus Univ.) [29]	1998–2009	7	ATTRv (all non-Val30Met mutations: Leu111Met mutations)	72%	71%	NR	6 simultaneous and 1 staged CHLT; cardiac rejection: 1 (14%) patient
Nagpal et al. (2013) (Cleveland Clinic) [34]	2006–2012	5	ATTRv ($n = 1$); HCV cirrhosis ($n = 4$)	100%	NR	NR	3-yr survival: 100%; all patients had cardiomyopathy; cardiac rejection: none
Atluri et al. (2014) (Univ. Pennsylvania) [35]	1997–2013	26	Cardiac cirrhosis ($n = 23$); HCV cirrhosis ($n = 2$); A1-ATD cirrhosis ($n = 1$)	87%	83%	NR	Cardiac rejection: 3 (11%) patients
Careddu et al. (2015) (Univ. Bologna) [36]	1999–2012	15	ATTRv ($n = 14$) (all non-Val30Met mutations); HCV cirrhosis ($n = 1$)	93%	83.3%	NR	Cardiac rejection (first year): none; DLT: 8 (53.3%) patients
Reich et al. (2015) (Cedars-Sinai Los Angeles) [37]	1998–2014	7	ATTRv ($n = 3$); cardiac cirrhosis ($n = 4$)	100%	NR	NR	6 simultaneous and 1 staged CHLT; cardiac rejection: none
Barbara et al. (2015) (Mayo Rochester) [38]	1999–2013	27	ATTRv ($n = 21$); other ($n = 6$)	96%			Liver first procedure (due to DSA): 2 patients; simultaneous kidney-heart-liver transplant: 4 patients; DLT: 12 (44%) patients
Suhr et al. (2016) (FAPWT Registry) [2]	1991–2012	52	ATTRv (all non-Val30Met mutations)	91%	NR	62%	38 simultaneous and 12 staged CHLT; 2 simultaneous kidney-heart lung transplant; better evolution of CHLT after 3-yr
Wong et al. (2016) (Mayo Rochester*) [39]	2004–2013	22	ATTRv ($n = 15$); cardiac cirrhosis ($n = 7$)	86.4%	86.4%	69.1%	Cardiac rejection: Tc/AMR: 7 (31.8%) patients; lower rejection rate compared to isolated HT: 189/223 (84.4%) patients ($P < 0.0001$); AMR: 1 (4.5%) versus 3 (14.8%) ($P = 0.004$)
Yi et al. (2018) (Methodist Houston) [40]	2004–2017	18	ATTRv; cardiac cirrhosis	100%	92.9%	NR	Cardiac rejection: none

* Data from same center highlighting different important aspects of CHLT. A1-ATD: alpha-1-antitrypsin deficiency; NR: not reported; ATTRv: hereditary transthyretin amyloidosis; DLT: domino liver transplantation; DSA: donor specific antibodies; Tc/AMR: T-cell/antibody mediated rejection; HCV: hepatitis C virus; HT: heart transplantation.

despite medical treatment indicates early heart transplantation (HT) or CHLT [2,3,6,13,19,26]. In such patients, neurologists and cardiologists should request priority status on both heart and liver waiting lists in order to avoid the dramatic outcomes as documented in three of the presented cases [29]. The Copenhagen experience with the "cardiogenic mutation" Leu111Met indeed showed that early LT may prevent the development of severe cardiomyopathy and the need for CHLT [30].

According to the International Society for Heart and Lung Transplantation Registry (ISHLT), ATTRv-amyloidosis is the most frequent indication for CHLT. CHLT offers a similar or even better survival compared to isolated LT and/or HT [2,10,13,31-43] (Table 1). The FAPWTR identified 80 HLT: 57 CHLT, 19 sequential HLT (17 LT after and 2 before HT) and 4 combined heart-liver-kidney transplants [2,10]. These HLT patients had 24 different mutations of which Val30Met and Thr60Ala were the most common. The 1-, 5- and 10-year survival rates were 85%, 75% and 53%, respectively. In the nine most common non-Val30Met mutations, cardiopathy was present in 44 (77%) patients and 21 (36.8%) patients required CHLT. The non-Val30Met FAPTRWR 2016 report allowed not only to identify those mutations that can benefit from an isolated LT but also mutations (e.g. Ser50Arg, Ser77Phe and Ser77Tyr) that do badly after CHLT, whereas others (e.g. Leu111Met, Thr60Ala, Glu84Gln) and the Val122del mutation do well if performed timely [2,44]. Early identification of these mutations and detection of cardiac amyloid deposition using modern imaging are thus of utmost importance as it has been shown that severely altered cardiac autonomic function does not improve in most patients after transplantation [7,9,43,45].

Of great interest is the confirmation by The International Society for Heart and Lung Transplantation data and other reports, that CHLT generates an important immunologic advantage [9,29]. The significantly reduced incidences of early allograft rejection and vasculopathy rates, compared to those of isolated HT, confirm the previously well documented protective role of the liver in combined organ transplantations [13,31,33,39,46,47] (Table 1). Despite this supplementary advantage, several teams propose a staged rather than a simultaneous HLT to reduce the incidence of renal dysfunction (linked to the use of cardiopulmonary bypass) and the use of blood products and inotropic medications [6,13,32,38,48,49].

Finally, a short note on DLT in the context of amyloidotic cardiac disease. The use of amyloidotic livers as a precious allograft source was introduced in 1995 by Furtado et al. [50]. Our small series showed that non-Val30Met ATTRv-amyloidosis patients require a complete hepatic evaluation including fibro-elastography in order to detect fibro-cirrhotic changes ("cardiac liver"). The presence of ascites should alert transplant physicians to explore the possible domino graft more in detail as fibrotic changes makes DLT impossible as shown here and in the Mayo experience [36,38,51,52].

In conclusion, ATTRv-amyloidosis is a rare disease caused by numerous TTR gene mutations. LT has been the gold-standard in the treatment of progressive disease for many years. Nowadays novel pharmacological treatments prevail as the initial treatment, reducing the role of transplantation to patients in which such treatments are unavailable or fail. The determination of the mutation is of utmost importance since disease penetrance, progression, therapeutic algorithm, timing and outcome of LT largely vary according to and within a single mutation. Compared to Val30Met patients, non-Val30Met mutations present with a clinical picture dominated by cardiac involvement. A case series of the very rare Val122del mutation comprising four patients, three of them needing HLT, is reported here for the first time in literature. Due to its aggressive behavior, symptomatic Val122del patients should be prioritized on both heart and/or liver transplant waiting lists to avoid rapidly (and eventually lethal) occurring cardiac and neurological damage. Good results can be obtained although sequential or simultaneous HLT is often necessary.

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None

CRediT authorship contribution statement

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Ethical approval

The study was approved by the respective institutional review board and performed in accordance with the 2000 *Declaration of Helsinki* and the 2008 *Declaration of Istanbul*.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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