**Name of Journal: *World Journal of Hepatology***

**ESPS Manuscript NO: 29879**

**Manuscript Type: Minireviews**

**Iatrogenic amyloid polyneuropathy after domino liver transplantation**

Mnatsakanova D *et al*. Iatrogenic amyloid polyneuropathy after domino transplantation

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**Author contributions**: Mnatsakanova D and Živković SA contributed equally to this work, generated the tables and wrote the manuscript.

**Conflict-of-interest** **statement:** The authors declare no conflicts of interest regarding this manuscript.

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**Manuscript source:** Invited manuscript

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**Received:** August 30, 2016

**Peer-review started:** September 1, 2016

**First decision:** September 29, 2016

**Revised:** October 14, 2016

**Accepted:** December 7, 2016

**Article in press:**

**Published online:**

**Abstract**

Liver transplantation has been used in treatment of transthyretin amyloidosis, and some patients undergo domino liver transplantation (DLT) with explanted liver being transplanted to another patient with liver failure as the liver is otherwise usually functionally normal. Until end of 2015, there were 1154 DLT performed worldwide. DLT for transthyretin amyloidosis is associated with the risk of developing *de novo* systemic amyloidosis and amyloid neuropathy, and the risk may be greater with some non-Val30Met mutations. *De novo* amyloid neuropathy has been described in up to 23% of transplant recipients. Neuropathy may be preceded by asymptomatic amyloid deposition in various tissues and symptoms of neuropathy started after a median of 7 years following DLT (5.7 ± 3.2 years; range 2 mo to 10 years). Typical initial symptoms include neuropathic pain and sensory loss, while dysautonomia usually starts later. Progression of neuropathy may necessitate liver re-transplantation, and subsequent improvement of neuropathy has been reported in some patients. Explant allograft recipients need close monitoring for signs of systemic amyloidosis, neuropathy and dysautonomia as progressive symptoms may require re-transplantation.

**Key words:** Transthyretin; Familial amyloid neuropathy; Domino liver transplantation; Acquired amyloid neuropathy; Systemic amyloidosis

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**Core tip:** Domino liver transplantation (DLT) has been used in treatment of transthyretin amyloidosis, with explanted liver being transplanted to another patient with liver failure as the liver is otherwise usually functionally normal. Domino liver explant recipients are at risk of developing *de novo* systemic amyloidosis and amyloid neuropathy has been described in up to 23% of transplant recipients after a median of 7 years following DLT. Typical initial symptoms include neuropathic pain and sensory loss, while dysautonomia usually starts later. Explant allograft recipients need close monitoring for signs of systemic amyloidosis, neuropathy and dysautonomia as progressive symptoms may require re-transplantation.

Mnatsakanova D, Živković SA. Iatrogenic amyloid polyneuropathy after domino liver transplantation. *World J Hepatol* 2016; In press

**INTRODUCTION**

Transthyretin familial amyloidosis is an autosomal dominant multisystem disorder caused by deposition of insoluble transthyretin (TTR) amyloid deposits in various tissues[1]. Amyloid deposits are found in peripheral nerve, liver, skin, heart and other organs, and peripheral neuropathy is one of the major clinical manifestations. Three main phenotypes of transthyretin familial amyloidosis include familial amyloid polyneuropathy (TTR-FAP), cardiomyopathy and leptomeningeal amyloidosis. Additionally, wild type TTR may be also deposited in senile systemic amyloidosis which more commonly presents with cardiomyopathy, and only rarely as neuropathy. TTR-FAP is a progressive sensorimotor neuropathy with dysautonomia which results in a severe disability. The neuropathy usually starts with distal sensory loss and dysesthesias, followed by autonomic dysfunction, while motor function is usually affected only later[2]. Carpal tunnel syndrome is usually an early feature, but there is a significant variability of symptoms, even among the patients with the same TTR mutation. Overall prevalence of TTR-FAP is estimated at 0.9-1.1 per 10000000 people, with expected survival of 7-12 years after the onset of symptoms[3-5]. To date more than 120 mutations of TTR have been reported to cause TTR-FAP, and high prevalence is found in endemic regions in Portugal, Japan and Sweden (up to 1 in 1000 to 1 in 10000), and the most common genotype with predominant neuropathy is Val30Met TTR mutation[6].

Transthyretin is mainly synthesized in the liver and liver transplantation has been used to ameliorate the progression of systemic amyloidosis by decreasing the synthesis of abnormal TTR[7,8]. There is a shortage of liver grafts available for transplantation, and explanted liver of the patient with TTR amyloidosis is sometimes transplanted to another patient with liver failure as the liver is otherwise usually functionally normal Domino liver transplantation (DLT)[8]. Until end of 2015, there were 1154 DLT s performed worldwide[9]. Best outcomes for liver transplantation have been reported in young Val30Met patients with mild symptoms, and the overall 20-year survival after liver transplantation for TTR-amyloidosis has reached 55%[8,10,11]. In transplant patients (DLT donors) with non-Val30Met genotype, there is a wide spectrum of survival rates which vary a lot depending on the underlying mutations[12]. The overall risk of amyloid production by transplanted domino liver was thought to be low with potential delayed manifestations of amyloidosis in patients with otherwise very short survival if they are not transplanted. Nevertheless, amyloid deposition in the tissue may start soon after domino transplantation and iatrogenic amyloid neuropathy may affect up to 8-24% of DLT recipients[13,14].

In this manuscript, we review clinical features of acquired amyloid TTR neuropathy after DLT.

**LITERATURE**

We have identified 16 case reports with detailed description of acquired TTR-FAP in recipients of DLT in the literature search (Table 1)[14-23]. The patients were 73% men with age of 60.7 ± 10.4 years. The most common TTR mutation was Val30Met (*n* = 10; 61.3%), and others included Ser23Asn, Ser77Tyr, Leu58His, Thr49Ala, Gly47Glu, Glu54Gly (*n* = 1 each; 6.7%). Underlying causes of liver failure include hepatitis C infection (*n* = 8), hepatocellular carcinoma (*n* = 6), hepatitis B infection (*n* = 5), primary sclerosing cholangitis, primary biliary cirrhosis and nonalcoholic liver steatosis (*n* = 1 each; some patients had more than 1 cause).

*De novo* amyloid neuropathy presented at after a median of 7 years following DLT (5.7 ± 3.2 years; range 2 mo to 10 years). Initial symptoms included neuropathic pain (*n* = 14), sensory loss (*n* = 5), erectile dysfunction (*n* = 2), weakness, diarrhea and orthostatic hypotension (*n* = 1, each). Nerve biopsies showed amyloid deposits in 3 reported cases[16,18,23]. Other abnormal tests included positive rectal and abdominal fat (*n* = 2 each), duodenal and endomyocardial biopsies (*n* = 1 each) showing amyloid deposits. Three patients were treated with retransplantation of the liver, with improved outcome in two patients (outcome not reported in the third case).

The age of donors and recipients of domino liver allografts was not associated with an earlier onset of amyloid neuropathy. Non-Val30Met TTR mutations were overall associated with earlier onset of *de-novo* TTR-FAP neuropathy (latency 3.95 *vs* 6.83 years after transplantation; range 2 mo to 10 years).

**CONCLUSION**

DLT has been advocated to alleviate shortage of liver allografts for patients in liver failure who would not have survived without such procedure. Initial reports estimated a low risk of systemic amyloidosis from synthesis of abnormal transthyretin liver allografts. Nevertheless, subsequent studies demonstrated that recipients of DLT are indeed at risk from systemic amyloidosis and some patients may develop *de-novo* amyloid neuropathy after a median of 7 years following transplantation (5.7 ± 3.2 years; range 2 mo to 10 years). Similarly, less favorable survival of patients with non-Val30Met after liver transplantations (domino liver donors) was paralleled by shorter latency of *de-novo* amyloid neuropathy in domino liver recipients with allografts with non-Val30Met TTR mutations (3.95 *vs* 6.83 years)[12]. Nevertheless, there seems to be a marked variability of clinical course, depending on the underlying TTR mutation in domino liver donors (and allografts). Exceptionally short latency of *de novo* amyloid neuropathy in DLT recipients was reported with Ser23Asn and Leu58His TTR mutations (< 6 mo)[14,19]. These series did not show an association with donor or recipient age with *de novo* systemic TTR amyloidosis, although other studies suggest that recipient aging may accelerate tissue deposition of amyloid[24].

Clinically, these patients typically present with sensory loss and neuropathic pain, while dysautonomia is often not the initial symptom and follows later (Table 1). Tissue deposition of amyloid in the gastrointestinal tract and skin may precede clinical symptoms of neuropathy by several years[20,25]. and prospective study showed deposition of amyloid in salivary glands in up to 48% of DLT recipients[14]. Additionally, amyloid deposits were also found on sural nerve biopsies in the absence of clinical signs of neuropathy (research study and autopsy)[13,26]. Transthyretin amyloid neuropathy in DLT recipients presents in the context of systemic amyloidosis and *de novo* amyloid produced by transplanted liver is also found in myocardium, gastrointestinal tract, skin and fatty tissues[15,17,19-22]. Autopsy case of a DLT patient with asymptomatic amyloidosis at 8 years after transplantation (died from lymphoma) showed amyloid deposits in the heart, lungs, gastrointestinal tract (upper and lower), pancreas, spleen, testes, epididymis, prostate, skeletal muscle, thoracic sympathetic ganglia and median nerve (carpal tunnel syndrome)[26]. Amyloid deposition in the myocardium after DLT is usually asymptomatic, and so far only two cases of *de novo* cardiomyopathy after DLT have been reported with Val71Ala and Val30Met mutations[27,28]. One of the patients developed cardiac amyloidosis 5 years after re-transplantation for systemic *de novo* amyloidosis after DLT, and it is unclear whether cardiac amyloidosis was related to wild-type or mutant transthyretin[28]. Similarly, DLT donors continue to have deposition of amyloid in different tissues of FAP-TTR patients after transplantation, which is at least partly related to wild-type (“senile”) amyloid[29]. Worsening of peripheral neuropathy after transplantation has been reported in 24% of DLT liver allograft donors[5], and ocular deposition of amyloid is not abated after liver transplantation, as mutant TTR continues to be synthesized in the retinal pigment epithelium[30].

While *de novo* amyloid neuropathy is associated with significant morbidity, DLT recipients may also have other potential causes of neuropathy and nerve biopsy may be needed to establish the etiology and exclude alternative etiologies[14]. Nevertheless, nerve biopsy may be false negative with a reported sensitivity of 33-80%, and this may be attributed to uneven distribution of amyloid along peripheral nerves[31-33]. Biopsies of gastrointestinal tract, myocardium and fat aspirate may also demonstrate systemic deposition of amyloid in DLT recipients[15,17,19-22].

*De novo* amyloid neuropathy presents in the context of systemic amyloidosis and careful monitoring of clinical manifestations of amyloidosis is needed after DLT (Table 2)[34]. Once iatrogenic amyloid neuropathy and systemic amyloidosis are diagnosed, treatment options are limited and retransplantation has been reported to stabilize or improve neuropathy in some recipients[15,16]. Tafamidis, a tetramer stabilizer, is approved for treatment of FAP-TTR in Europe, Japan, Mexico and Argentina and is used as first-line treatment for early FAP-TTR[35]. In countries where tafamidis is available, liver transplantation is often considered as a second-line option for patients who progressed on tafamidis or did not tolerate the treatment. Liver-retransplantation typically carries worse prognosis and more significant morbidity than the initial transplantation, but the survival after liver retransplantation in DLT recipients seems to be greater than in other subgroups of liver retransplant recipients[36]. Despite a single report of benefits with deflunisal[37], potential benefits of treatment with tetramer stabilizers in DLT recipients remain uncertain. There are also no reports on efficacy of inhibition of expression of TTR gene in this setting. At this time, tafamidis remains available in a limited number of countries, and new experimental treatments are still not ready to substitute the role of DLT in treatment of systemic amyloidosis. In conclusion, DLT is associated with the risk of developing *de novo* systemic amyloidosis and amyloid neuropathy, and the risk may be greater with some non-Val30Met mutations. Explant allograft recipients need close monitoring for signs of systemic amyloidosis, neuropathy and dysautonomia as progressive symptoms may require re-transplantation.

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**P-Reviewer:** Schmidt HHJ **S-Editor:** Qiu S **L-Editor: E-Editor:**

**Table 1 *De novo* transthyretin amyloid neuropathy cases after liver transplantation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **TTR mutation** | **Age at transplant** | **Latency (yr)** | **Cause of liver failure** | **Initial Neuropathy symptoms** |
| [14] | Val30Met | 61 | 8 | HCV EtOH | Pain |
| [14] | Val30Met | 35 | 5 | HBV | Pain |
| [14] | Val30Met | 26 | 3.5 | HCC | Pain, erectile dysfunction |
| [14] | Val30Met | 28 | 5 | HBV | Pain |
| [14] | Ser77Tyr | 57 | 2 | HCC HBV HCV | Pain |
| [14] | Leu58Hys | 60 | 0.17 | HCV HIV | Pain, weakness |
| [14] | Thr49Ala | 49 | 2 | HCC HCV | Pain, orthostatic hypotension |
| [15] | Glu54Gly | 43 | 9 | HCC | Diarrhea, pain, sensory loss |
| [16] | Val30Met | 60 | 7 | HBV cirr | Pain |
| [17] | Gly 47Glu | 65 | 10 | HCC | Pain |
| [18] | Val30Met | 54 | 9 | HCV | Pain, erectile dysfunction |
| [19] | Ser23Asn | 72 | 0.5 | NASH | Sensory loss, pain |
| [20] | Val30Met | 50 | 7 | PBC | Sensory loss |
| [21] | Val30Met | 35 | 10 | PSC | Pain, sensory loss |
| [22] | Val30Met | 59 | 12 | HBV HCV cirr | Pain, sensory loss |
| [23] | Val30Met | 47 | 8 | HCV cirr | Pain |

PBC: Primary biliary cirrhosis; NASH: Nonalcoholic hepatic steatosis; EtOH: Alcoholic liver cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; cirr: Cirrhosis of the liver; PSC: Primary sclerosing cholangitis.

**Table 2 Evaluation and monitoring of possible *de novo* amyloidosis after domino liver transplantation**

|  |  |  |
| --- | --- | --- |
| **Clinical presentation** | **Signs and symptoms** | **Testing** |
| Dysautonomia (small fiber neuropathy) | Orthostatic hypotension  Sweating abnormalities (anhidrosis)  Constipation/diarrhea  Erectile dysfunction  Neuropathic pain  Arrhythmia  Neurogenic bladder | Tilt table testing  QSART with autonomic battery  ECG  Neurologic examination |
| Large fiber polyneuropathy | Sensory loss  Weakness  Neuropathic pain  Ataxia  Areflexia | EMG/NCS  Nerve (and muscle) biopsy  Neurologic examination |
| Cardiac amyloidosis | Fatigue  Arrhythmia  Syncope  Orthostatic hypotension | ECG  Transthoracic echo  Radionuclide imaging  Cardiac MRI  Endomyocardial biopsy  BNP/troponin |
| Gastrointestinal amyloidosis | Constipation/diarrhea  Nausea/vomiting | GI tract biopsy |
| Ocular amyloidosis | Dry eye  Vitreous opacity  Glaucoma | Ophthalmologic evaluation |
| Leptomeningeal amyloidosis | Cerebral infarction/hemorrhage  Hydrocephalus  Ataxia  Spastic paresis  Seizures  Dementia | MRI of brain and spinal cord  Meningeal biopsy |
| Other system involvement | Coldness  Weight loss  Peripheral edema  Anemia  Dry mouth | Rectal and abdominal fat biopsy  Salivary gland biopsy  TSH  Urinalysis/urine protein collection |