Peroneal Neuropathy Following Liver Transplantation: Possible Predisposing Factors and Outcome

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Abstract

Introduction: **Perioperative peroneal neuropathy is an uncommon complication following operations remote from the leg or in supine position including liver transplant.**

Materials and Methods: **We retrospectively reviewed the medical records of 132 living-donor liver transplant recipients done at our center between September 2006 and December 2008. Various potential preoperative, intraoperative, and postoperative factors were studied in the cases that developed perioperative peroneal neuropathy.**

Results: **Peroneal neuropathy was reported in 7 recipients (5.3%) following liver transplant. Apart from intraoperative positioning, other identifiable predisposing factors appear to be poor nutritional status, tall and slender body shape, alcoholic liver disease, and higher pretransplant model for end-stage liver disease score. All patients were treated conservatively, including nutritionally balanced diet and vitamin supplements combined with physical rehabilitation therapy. The motor power returned to normal within 6 months in all 7 patients.**

Conclusions: **Perioperative peroneal neuropathy may be contributed by various preoperative factors apart from intraoperative nerve compression. It can be effectively prevented by being aware of the predisposing factors and implicating adequate precautions perioperatively.**

Key words: *Perioperative, Foot drop, Chronic liver disease, Malnutrition*

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Perioperative peroneal neuropathy is a well-recognized complication, following prolonged surgery in the lithotomy position (1, 2). This is due to anatomic vulnerability of peroneal nerve to compression, traction, or ischemia during intraoperative leg positioning. Its likelihood in relation to operations remote from leg, or in the supine position, like cardiac surgery (3) and abdominal surgeries including liver transplant (4-10), advocate the role of other factors. In this manuscript, we discuss the various factor(s) that may have predisposed the patient to peroneal neuropathy after liver transplantation.

Materials and Methods

We retrospectively reviewed the hospital database of 132 liver transplants recipients (106 men and 26 women) who underwent a first living-donor liver transplant at our center between September 2006 and December 2008. Distribution of all recipients, depending on the cause of end-stage liver disease, is shown in Table 1.

Table 1. Causative distribution of patients with perioperative peroneal neuropathy among all LDLT recipients.

Cause of liver failure	Number of patients	Peroneal neuropathy
HCV	33	1
Alcohol	29	4
Cryptogenic	20	0
HCV + HCC	9	0
HBV	11	0
Cholestatic liver disease *	11	0
HBV + HCC	5	0
Alcohol + HCV	2	2
Fulminant hepatic failure **	7	0
Wilson disease	1	0
Autoimmune	2	0
HCC	1	0
Neonatal hepatitis	1	0

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
*Progressive familial intrahepatic cholestasis, Primary biliary cirrhosis, extrahepatic biliary atresia, Caroli's syndrome, Portal biliopathy
**Viral hepatitis (hepatitis E virus, acute hepatitis B virus); Wilson disease; cryptogenic

All recipients diagnosed with perioperative foot drop were studied in detail. None of the patients had symptomatic peroneal neuropathy preoperatively. Preoperative variables collated were age, sex, weight loss in last 6 months, body mass index, cause of liver disease, model for end-stage liver disease score, and history of any associated comorbid illness that may predispose to peripheral neuropathy like diabetes or any neurologic disease. Serum cholesterol was reviewed as a miscellaneous variable (as a marker of nutritional status).

Intraoperatively, all patients were placed in supine position with adequate padding around the knee joints. The only operative variable studied was duration of surgery. Postoperatively, all recipients were nursed in the transplant intensive care unit and were seen by internist, surgical team, and hepatologist regularly. As per the unit protocol, triple immunosuppression regimen consisting of steroids, tacrolimus, and mycophenolate mofetil was used in all recipients. The only postoperative variable analyzed was serum tacrolimus level. All recipients received tacrolimus (0.05 mg/kg/d in 2 divided doses) from the evening of the first postoperative day. The first serum tacrolimus level was done after the first 5 dosages of tacrolimus, and then the dosage was adjusted accordingly to maintain a trough level between 4 and 8 ng/mL.

Detection of weakness in foot, either by patient or during routine examination, led to detailed neurologic examination and an opinion from a neurologist. After excluding the other causes clinically and through biochemical tests (including serum electrolytes, tacrolimus level), all patients were managed conservatively in consultation with neurologist.

Results

Seven recipients (all men; aged, 38-60 years) were clinically diagnosed in perioperative peroneal neuropathy resulting with an incidence of 5.3% (7/132) (Table 2). All patients who developed foot drop had history of weight loss more than 15 kg (range, 15-24 kg) within the last 6 months before transplant. All were tall and slender, having a body mass index of less than 20 kg/m^2 despite pedal edema and ascites. All of them had a model for end-stage liver disease score of > 25 (range, 26-30). Six patients (85.7%) had a primary diagnosis of alcoholic liver disease including 2 patients who also were positive for HCV. Two patients had raised serum glucose levels during pretransplant evaluation phase and were managed accordingly. All patients were diagnosed within 3 days after the transplant (usually, when they were ambulated). One patient complained of weakness on postoperative day 1, 2 on postoperative 2, and 4 on postoperative 3. Six developed unilateral foot drop; 1 had it bilaterally. Interestingly, 5 of 7 patients (71.4%) developed it on left side. In all 7 patients, the first serum tacrolimus level ranged from 1.7 to 5.2 ng/mL.

Table 2. Risk factors studied among patients with perioperative peroneal neuropathy.

Sex/Age (y)	M/60	M/48	M/55	M/38	M/41	M/50	M/48
Cause	Ethanol	Ethanol	Ethanol +HCV	Ethanol	Ethanol +HCV	HCV	Ethanol
MELD score	27	26	29	29	28	27	30
Height (m)	1.83	1.81	1.77	1.76	1.77	1.8	1.78
Weight (kg)	64	62	60	56	57	60	56
Weight loss (kg)*	> 20	16	24	20	>20	15	18-20
Body mass index (kg/m^2)	19.11	18.92	19.15	18.07	18.19	18.51	17.67
Comorbid illness	Absent	Absent	Diabetes	Absent	Diabetes	Absent	Absent
Operative time (h)	14	12	11	16	15	14	12
Foot drop (side)	Right	Left	Left	Left	Bilateral	Left	Left
Day of manifestation	3	1	2	3	3	3	2
First serum tacrolimus level (ng/mL)	2.3	3.4	1.7	2.1	4.3	5.2	3.2

*Weight loss within 6 months before transplant
Abbreviation: HCV, hepatocellular carcinoma; MELD, model for end-stage liver disease

All patients were treated by conservative means, which included a nutritionally balanced diet and vitamin supplements combined with physical rehabilitation therapy. They were made to walk with foot splint, gradually from support, to without support. The motor power of all 7 patients returned to normal within 6 months.

Discussion

Peroneal neuropathy is an infrequent, but the most-common perioperative mononeuropathy, in surgical patients. Although most perioperative mononeuropathies are associated with intraoperative malposition during colorectal, gynecologic, urologic, and joint surgery close to peroneal region (1, 2); a recent study reported that they can occur during any operation, of any duration (8). Its incidence following

orthotopic liver transplant has been reported to range from 1.4% to 13.3% (4-6); however, the risk factors predisposing it in liver transplant are not yet understood.

The foremost alleged cause is prolonged nerve compression around the fibular head. In the present study, the average operative time among patients who developed perioperative peroneal neuropathy was 13.4 hours compared to 14 hours for all liver transplants done during this period. During liver transplant, the nerve may be compressed between the fibular head and the operating table, with the patient lying in an anatomic supine position. In this position, the lateral surface of knee, leg, lateral malleolus, and foot remain in direct contact with operating table. The contact pressure is further enhanced by frequent sideways tilting of operating table required to facilitate the mobilization of native liver. The other possibility might be an incorrect posture of surgical assistants that make them lean their body against the patient's knee. Additionally, the nerve could be compressed from an intraoperative application of intermittent pneumatic compression devices used for prophylaxis of deep vein thrombosis (11). However, the absence of peroneal neuropathy in living-liver donors who also undergo a prolong surgery (8-10 h), along with changes in position of the operating table, led us to consider the potential role of other factors. Furthermore, we could not ascertain the role of the intermittent pneumatic compression devices as they were applied to all donors and recipients at our center.

In this study, patients who developed peroneal neuropathy were tall, slender (body mass index < 20 kg/m^2), and had a history of severe and rapid weight loss (> 15 kg in 6 months). Their preoperative serum cholesterol levels were between 35 and 56 mg/dL. This indicates the severity of malnutrition, and a rapid deterioration in their general health. It may be prudent to comment that the poor nutritional status of these patients, having minimal subcutaneous pad of fat, positions them at increased risk for nerve compression. Though our study lacks data for exact duration of tilt on each side; nevertheless, it was definitely more on left side, as more time is required to mobilize the right lobe of liver.

Chronic liver disease is an independent cause associated with peripheral sensorimotor and autonomic polyneuropathy, being more common in patients with alcoholic liver cirrhosis (12, 13). The incidence varies from no neuropathy to over 90%. It is subclinical or mild in most of the patients, and can be detected only on electrophysiologic testing (13). A study has noted symptomatic neuropathy in 16.2% patients, whereas electroneurography (ENG) was abnormal in 48.6% (14). As neuropathy is primarily determined by metabolic dysfunction caused by liver disease (rather than the cause of liver disease), these dysfunctions correlate well with severity of liver disease. During the study period, the median model for end-stage liver disease score among all liver transplant recipients and recipients who developed peroneal neuropathy was 23.4 and 28. Presence of relatively higher model for end-stage liver disease score among patients with peroneal neuropathy led us to contemplate that varying degree of asymptomatic neuropathy must have been present pretransplant in these patients. This is more than an assumption, as 85.7% of these patients were chronic alcoholics. Neuropathy was reported to be more severe in Child's class C than in class B cirrhosis (15). Various postulated mechanisms for metabolic dysfunction in nerve are metabolic inhibition of the axonal membrane function, metabolic damage to Schwann cells, and even a possible disordered insulin metabolism, similar to diabetic neuropathy (13, 14). In alcoholics, this may be contributed to by associated poor nutritional status, vitamin deficiencies (thiamine), the direct toxic effect of alcohol on peripheral nerves, and exposure to heavy metals, like lead and neurotoxic industrial agents (14). Interestingly, none of the patients who undergone a liver transplant for acute liver failure developed it. The role of contemporaneous presence of hepatitis C virus infection in 2 patients could not be ascertained.

Renal dysfunction associated with advanced chronic liver disease may also result in slowing of nerve conduction velocity. More than 50% of patients had abnormal nerve conduction velocity when creatinine clearance < 10 mL/min (16). Another important cause may be drug toxicity. Tacrolimus has been reported to cause peripheral neuropathies; however, they are the least common and late adverse events (17). In the present study, the serum tacrolimus levels in patients with peroneal neuropathy were 1.7 to 5.2 ng/mL, which is well within the normal range. Furthermore, all

neuropathies were reported by the third postoperative day.

Nerve conduction and electromyographic studies are not necessary when a definite compressive episode can be identified; however, they should be done whenever there is a concern about the cause of peroneal neuropathy or a patient does not show any sign of improvement (18). They also have a potential role in predicting the recovery. All patients were treated by conservative means including nutritionally balanced diet, vitamin supplements (especially vitamin B6 and B12) combined with physical rehabilitation therapy (both active and passive). They were made to walk with foot splint, initially with support, and than gradually without support. The motor power in all patients returned to normal within 6 months, as seen in many studies (1, 4, 5, 8, 10). To prevent this in future, we made a protocol to apply gel pads along with extra cotton padding around the knee, especially laterally. Apart from minimizing the tilting of operating table, the introduction of fixing both feet in dorsiflexion resulted in no peroneal neuropathy among the last 92 liver transplants done at our center. This maneuver decreases the contact between operating table and lateral surface of knee. Simultaneously, we recommend providing working knowledge of anatomy and physiology, patient risk factors, injury mechanisms, potential complications, and positioning devices required in perioperative positioning to all the perioperative team members including assisting nurses.

Being a retrospective study, our study has few limitations. The study lacks the data for body mass index, tacrolimus level, status of renal function including glomerular function rate of recipients who did not develop peroneal neuropathy. The study also lacks the data for history of alcohol intake for patients diagnosed with nonalcoholic, chronic liver disease. None of the peroneal neuropathy patient had undergone any electrophysiologic studies to confirm the cause and severity of neuropathy. Though we mentioned various preoperative, intraoperative, and postoperative factors; we could not ascertain the percentage contribution of each factor. However, studies such as these remain important as the predisposing factors found to be contributory are frequent in patients with advanced chronic liver disease.

Conclusion

Perioperative peroneal neuropathy is a rare but a possible complication following liver transplant. Apart from intraoperative positioning, other identifiable predisposing factors appear to be poor nutritional status; tall and slender body shape; alcoholic liver disease; and high model for end-stage liver disease score. Though it has a good prognosis, it can be debilitating in patients with bilateral involvement. It can be effectively prevented by being aware of the predisposing factors and implicating adequate precautions perioperatively.

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