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Case Report

Rehabilitation of four patients with critical illness polyneuropathy following living-donor liver transplantation

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ABSTRACT

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Reports of critical illness polyneuropathy (CIP) following liver transplantation (LT) are rare, and rehabilitative approaches for CIP after LT have yet to be described in detail. Four patients who underwent living-donor LT developed extremity and/or respiratory muscle weakness after LT, suggesting of CIP. Rehabilitation was initiated at the bedside to prevent joint contracture, disuse muscle weakness, and pulmonary complications. Exercise intensity was increased gradually according to a set of safety indices. Electrophysiologic studies demonstrated motor-dominant axonal degenerations in extremities of all patients. Although no patient recovered fully by rehabilitation, all patients achieved gradual improvement in muscle strength, ability to walk with or without aid, and a final Barthel index score of 90. CIP is an important complication following LT, and should be suspected in patients who develop post-transplant muscle weakness in the extremities or respiratory muscles. The present results suggest that early rehabilitation after LT prevents secondary disuse syndrome and contributes to achieve favorable functional outcome.

Key words: living-donor liver transplantation, rehabilitation, critical illness polyneuropathy, functional outcome, exercise load

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Introduction

Severe muscle weakness that cannot be explained by disuse muscle atrophy alone often occurs in critically ill patients [1], and sometimes manifests early as difficulty in weaning from mechanical ventilation. This condition is named critical illness polyneuropathy (CIP), but many issues regarding the pathogenesis, treatment, and differential diagnosis remain unsolved [2]. As for functional outcome, even though survivors may not recover fully, they are able to walk with or without aid [3−6].

The incidence of CIP after liver transplantation (LT) has been reported to be 10% [7], and the risk of CIP is high in LT recipients with underlying conditions such as acute liver failure and immunodeficiency. However, there are few reports on CIP after LT with CIP [7, 8]. In addition, rehabilitation approaches for CIP have not been described in detail.

In this report, we describe the rehabilitation therapy of four patients who developed CIP following living-donor LT (LDLT) which was diagnosed by clinical features and electrophysiologic examinations. Since some articles cited in this report include cases of brain-dead LT, we cited the references as 'liver transplantation (LT)' unless living-donor is specially mentioned.

Case reports

Four patients who were referred to our department for rehabilitation after LDLT showed weakness in four extremities and/or respiratory muscles, suggesting CIP (Table 1). Patient 1 underwent surgical resection of suprasella tumor at 11 years of age, and received radiotherapy and chemotherapy for recurrence at age 13. Nonalcoholic steatohepatitis was diagnosed at age 15. One month later, he developed hepatopulmonary syndrome (HPS). Pulmonary perfusion imaging with technetium 99m-labeled macroaggergated albumin (^{99m}Tc-MAA) showed 57% pulmonary arteriovenous shunt without focal defect. Three months later, he

Table 1. Clinical and demographic details of four patients with CIP.

Patient	1	2	3	4
Age, Sex	15 year-old male	29 year-old male	64 year-old female	55 year-old female
Primary disease	HPS, LC, NASH	LC, PSC	Cryptogenic LC	HCC, LC, HCV
BMI at admission (kg/m^2)	27.1	24.2	18.1	39.4
Child-Pugh class	B 8	C 12	C 13	C 12
Reoperation after LT	1	2	3	0
Immunosuppressants	FK 506, basiliximab	Cyclosporine, basiliximab	FK 506, basiliximab	FK 506, basiliximab
Methylprednisolone (first dose)	250 mg	375 mg	375 mg	375 mg
Duration of muscle relaxant use	10 days (VB)	1 day (VB)	1 day (VB)	8 days (VB)
Peak serum CK (IU/l)	1045 (Day 1)	Normal range	1907 (Day 1)	2964 (Day 1)
End of mechanical ventilation	Day 7	Day 14	Day 78	Day 55
End of ICU stay	Day 15	Day 21	Day 87	Day 57

Day 0 is the day of transplantation.
HPS, hepatopulmonary syndrome; LC, liver cirrhosis; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; BMI, Body mass index; VB, vecuronium bromide; CK, creatine phosphokinase; ICU, intensive care unit.

received LDLT from his mother.

Patient 2 was diagnosed with primary sclerosing cholangitis at 22 years of age. At age 28, he had upper gastrointestinal bleeding from esophageal varices. Two months later, he received LDLT from his wife.

Patient 3 had upper gastrointestinal bleeding from esophageal varices, and was diagnosed with cryptogenic liver cirrhosis at 61 years of age. Because of gradual deterioration of liver function, she underwent LDLT from her sister.

Patient 4 was diagnosed with cirrhosis by hepatitis C at 49 years of age, and with hepatocellular carcinoma at age 54. Six months later, she underwent LDLT from her husband.

Prior to LDLT, three patients were able to walk outdoors, while Patient 1 was able to walk indoors only because of HPS. There was no history of alcoholic and diabetic peripheral neuropathy in all four patients.

Corticosteroids and immunosuppressants were initiated immediately after transplantation. Vecuronium bromide was administered during mechanical ventilation from day 1 to day 10 following transplantation. Patient 1 to 3 underwent reoperations because of portal vein stenosis in Patient 1, hepatic artery thrombosis in Patient 2, and portal vein reflux in Patient 3. No patient underwent retransplantation. Patient 2 developed acute renal failure and serum creatinine level was elevated to 4.2 mg/dL on the third post-transplant day. There was no evidence of sepsis based on bacteriologic examination, and aminoglycoside was not used.

The patients were referred for rehabilitation between 16 and 38 days after LDLT (Table 2). Barthel index [9] that measures activities of daily living (ADL) ranged from scores of 0 to 20. Two patients were still on mechanical ventilation. Distal dominant muscle weakness in four extremities and diminished deep tendon reflex in upper and lower extremities were observed in all patients. Patients 1 and 2 showed distal-dominant sensory disturbances and muscle atrophy, while sensory disturbance could not be evaluated in the other two patients because of severe edema.

We suspected CIP based on clinical findings and prescribed rehabilitation 5 times a week with the primary goal to prevent joint contracture, disuse muscle weakness, and pulmonary complications. We gradually increased the exercise intensity as the patient's general condition improved and neuromuscular recovery progressed. Once the patient was capable of sitting independently for 5 minutes, we started standing and walking training at the bedside.

We determined the exercise intensity according to the indices reported previously [10, 11]:

- Heart rate not exceeding 75 to 80% of the estimated maximum heart rate.
- Oxygen saturation of peripheral artery not lower than 90%.
- Perceived exertion not exceeding scores 12–13 on the Borg scale [12].
- No signs of exercise overload, such as excessive muscle pain and sudden muscle weakness.

In addition, because Patient 1 had postural hypoxemia, he underwent exercise in a supine position as reported previously [13] at a higher oxygen flow rate (maximum 10 L/min oxygen by nasal mask) than the other three patients.

To evaluate CIP, we performed electrodiagnostic tests between day 42 and day 193 after LDLT. Nerve conduction studies were carried out according to the methods described by Kimura [14]. These tests showed decreased amplitudes of compound muscle action potentials and sensory nerve action potentials, and delayed F wave latencies (Table 3). Needle electromyography was performed in Patients 3 and 4 (Table 4), but was contraindicated in Patients 1 and 2 who had thrombocytopenia. The muscles studied were deltoid, abductor pollicis brevis, first dorsal interosseous,

Table 2. Clinical evaluations at referral for rehabilitation and at the end of rehabilitation.

Patient	1	2	3	4
Referral for rehabilitation	Day 17	Day 29	Day 38	Day 16
Oxygen / Mechanical ventilation	8L/min by mask	2L/min by cannula	SIMV	SIMV
Bed rest level	Rest in bed	Rest in bed	Absolute rest	Absolute rest
MMT of U/E (proximal / distal)	2−3 / 1−2	3−4 / 3	1+ / 1	1 / 0
MMT of L/E (proximal / distal)	2 / 1−2	3 / 2	1+/ 1	1 / 0
Muscle atrophy	Left FDI and bilat. TA	Bilat. FDI and TA	NA due to edema	NA due to edema
Sensory disturbance, numbness	Bilat. hand, dorsum pedis, and lateral side of leg	Bilat. hand, dorsum pedis, and lateral side of leg	NA due to edema	NA due to edema
Barthel index score	5	20	0	0
End of rehabilitation	Day 147	Day 55	Day 246	Day 203
Reason for termination	Transfer to other facility	Infection of liver graft	Discharge from hospital	Discharge from hospital
MMT of U/E (proximal / distal)	3−4 /2−3	4−5 / 4	4 / 3−4	4 / 3−4
MMT of L/E (proximal / distal)	4 / 4	4−5 / 4	4 / 3−4	4−5 / 3−4
Sensory disturbance, numbness	Bilat. dorsum pedis	None	None	None
Walking aid	Walker, 5L/min O_2 by mask	None	None	None
Gait endurance (m)	15	400	100	100
Barthel index score	75	90	85	90

Day 0 is the day of liver transplantation.
SIMV, synchronized intermittent mandatory ventilation; MMT, manual muscle testing using a scale of 0 (none) to 5 (normal); U/E, upper extremity; L/E, lower extremity; FDI, first dorsal interossei; TA, tibialis anterior; Bilat, bilateral; NA, not assessable.

Table 3. Nerve conduction studies.

Nerve		Test	Normal range	Patient 1	Patient 2	Patient 3	Patient 4
R/L median nerve	MCS	Amplitude - APB (mV)	3.5 <	~ / 1.3	~ / 9.9	~ / 2.1	4.1 / 2.0
		Distal latency (ms)	< 4.2	~ / 3.4	~ / 3.0	~ / 4.1	4.3 / 3.8
		Conduction velocity - forearm (m/s)	48 <	~ / 52.5	~ / 61.8	~ / 54.9	54.4 / 57.7
		F wave latency / Height (ms/m)	< 16.5	~ / ~	~ / 15.7	~ / 16.9	15.6 / 15.8
R/L median nerve	SCS	Amplitude (μV)	19 <	~ / ~	~ / 27.3	~ / 41.1	29.2 / 14.1
		Distal latency (ms)	< 3.5	~ / ~	~ / 2.5	~ / 3.4	2.9 / 3.2
R/L ulnar nerve	MCS	Amplitude - ADM (mV)	2.8 <	~ / 1.5	~ / 5.9	~ / 3.4	~ / 6.2
		Distal latency (ms)	< 3.4	~ / 3.2	~ / 3.1	~ / 3.4	~ / 2.8
		Conduction velocity - forearm (m/s)	49 <	~ / 44.3	~ / 52.6	~ / 51.9	~ / 55.1
		F wave latency / Height (ms/m)	< 16.5	~ / 18.3	~ / 16.2	~ / 16.9	~ / 15.0
R/L ulnar nerve	SCS	Amplitude (μV)	18 <	~ / 3.3	~ / 27.9	~ / 13.7	~ / 18.4
		Distal latency (ms)	< 3.1	~ / 2.9	~ / 2.7	~ / 2.5	~ / 2.8
R/L tibial nerve	MCS	Amplitude - AH (mV)	2.9 <	NE / NE	11.8 / 10.1	5.2 / 5.7	~ / 3.3
		Conduction velocity - leg (m/s)	41 <	NE / NE	44.0 / 46.2	39.7 / 38.0	~ / 41.4
		F wave latency / Height (ms/m)	< 29	NE / NE	27.0 / 25.8	32.5 / 32.5	~ / 33.6
R/L peroneal nerve	MCS	Amplitude - EDB (mV)	2.5 <	0.35 / 0.31	0.22 / 0.70	0.57 / 1.3	~ / 0.76
		Conduction velocity - leg (m/s)	40 <	45.5 / 41.9	30.1 / 35.2	37.9 / 41.5	~ / 45.4
R/L sural nerve	SCS	Amplitude (μV)	6 <	~ / 3.4	8.1 / NE	3.0 / 5.3	~ / 3.0
		Distal latency (ms)	< 3.4	~ / 2.0	2.8 / NE	2.9 / 3.1	~ / 3.5
Time of electrophysiologic study				Day 42	Day 52	Day 193	Day 115

Day 0 is the day of transplantation.
R/L, right / left; MCS, motor conduction study; SCS, sensory conduction study; NE, not evoked; APB, abductor pollicis brevis; ADM, abductor digiti minimi; AH, abductor hallucis; EDB, extensor digitorum brevis; "~", not tested.

Table 4. Concentric needle electromyography.

Patient	Muscle	Spontaneous activity			Voluntary contraction			Interferencepattern
		Fib	PSW	Others	Amplitude (mV)	Duration (msec)	Polyphasicity	
3	L TA	+2	+4	–	0.3–1.0	6–20	+2	+2 ~ +3
	R GC	+1	+3	–	0.4–2.0	5–15	+1 ~ +2	+3
	L FDI	+2	+4	–	0.4–2.5	10–30	+3	+2 ~ +3
	L APB	+3	+4	–	0.3–1.5	5–15	+2	+3
	R TA	+2	+3	–	0.4–1.8	6–15	+2	+3
4	L Deltoid	–	+1	–	0.3–1.5	4–10	+1	+3
	L APB	+1	+1	CRD(+)	0.5–3.0	4–12	+1	+3
	L TA	–	+1	–	0.3–2.0	5–15	+2	+3
	L GC	–	+1	CRD(+)	0.4–1.6	4–10	+1	+3
	L Iliopsoas	–	+1	–	0.3–1.5	4–10	+1	+3
	R TA	–	+1	–	0.4–2.0	4–12	+2	+3

L, left; R, right; TA, tibialis anterior; GC, gastrocnemius; FDI, first dorsal interossei; APB, abductor pollicis brevis; Fib, fibrillation potential; PSW, positive sharp wave; CRD, complex repetitive discharge.
Semiquantitative grade of spontaneous activity: +1 rare; +2 occasional; +3 frequent; +4 abundant (according to Kimura [14] p. 346).
Semiquantitative grade of polyphasicity: 0 (none) to +4 (all motor units tested).
Semiquantitative grade of interference pattern: 0 (no motor unit) to +4 (normal).

iliopsoas, tibialis anterior, and gastrocnemius muscles. In both Patients 3 and 4, abnormal spontaneous activities, an increase in polyphasic motor unit action potentials, and a decrease in interference patterns were observed in all the muscles studied. But no myopathic motor unit was detected. These electrophysiologic findings suggested that motor-dominant axonal degeneration of peripheral nerves was the major pathology involved. Muscle and nerve biopsies were considered to be contraindicated [2] and therefore not done. Consequently, other causes of muscle weakness, such as acute inflammatory demyelinating polyneuropathy, critical illness myopathy, muscle relaxants, and immunosuppressants could not be ruled out.

The duration of rehabilitation ranged from 26 to 208 days, although exercises were sometimes interrupted by infections. All patients showed gradual improvement in muscle strength and were able to walk for 15 to 400 m, but residual muscle weakness persisted (Table 2). The patients were almost independent in ADL (Figure 1). In Patient 1, although pulmonary arteriovenous shunt decreased to 25%, he had residual HPS and required a walker and supplemental oxygen at the end of rehabilitation therapy.

Three patients presented for follow-up after rehabilitation therapy. Patient 1 visited at 192 days after LDLT. He was able to walk without aid, with a Barthel index score of 90. Patient 3 presented for follow-up at 277 days after LDLT, with a Barthel index score of 90. On the other hand, Patient 2 who discontinued rehabilitation because of graft infection died at 297 days after LDLT.

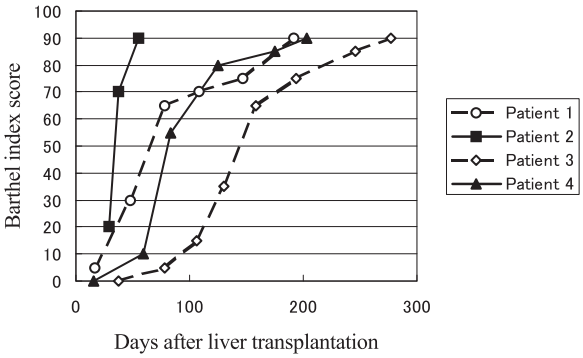

Figure 1. Changes in Barthel index score over time after liver transplantation in four patients.
In all patients, the Barthel index scores are low at referral for rehabilitation and eventually increase to 90, although the period of rehabilitation required differs among patients.

Discussion

Rehabilitation therapy early after LT is conducted concomitant with medical management to prevent three major complications; rejection, infection, and thrombosis, with due attention paid to the bleeding tendency and limitation of body position for graft establishment. The reduced exercise tolerance after patients are permitted to leave bed is an issue [15].

CIP not only delays weaning from mechanical ventilation, but may also cause secondary complications such as joint contractures, and hinder improvement of ADL and exercise tolerance during a

period when physical activity should be promoted. In fact, the four patients in this report showed delayed weaning from mechanical ventilation (7−78 days after LDLT), and slower improvement of Barthel index score compared with a previous report [16].

There are no established criteria regarding the optimal timing to initiate rehabilitation and the exercise intensity for CIP after LT. The present four patients were referred for rehabilitation relatively late, between day 16 and day 38 following LDLT, after the onset of CIP. When CIP is suspected, it is important to initiate rehabilitation therapy as soon as possible to address neuropathy. At the same time, attention has to be paid to the effect of exercise overload on neuropathy. A previous research that evaluated the effect of aerobic exercises at Borg index below 15 three times a week for 24 weeks in patients with familial amyloidotic polyneuropathy who underwent LT 2 to 12 months before the study showed improvements of body composition and walking capacity [17]. In the present study, exercise intensity was determined by monitoring heart rate, peripheral blood oxygen saturations and perceived exertion (Borg scale), which are indices of exercise intensity conventionally used in patients with liver dysfunction [10, 11, 18]. As we did not experience any adverse effect by exercises, these indices appear to be useful to determine exercise intensity even in patients with CIP after LT.

The prognosis of CIP is variable, and complete recovery from CIP may be delayed for over 2 years [5, 6]. Patients who survive have relatively good functional outcome. However, while most patients regain walking ability, residual problems of functional disability and social disadvantage remain even after one year [3], therefore continuous rehabilitation is necessary [19]. As for CIP following LT, the time required for functional recovery varies among two previous reported cases [7, 8] and the present four cases.

Patient 2 accomplished a Barthel index score of 90 earlier than the other three patients, was weaned from mechanical ventilation earlier than Patients 3 and 4, and had milder muscle weakness and nerve conduction abnormalities than the other three patients. These findings suggest that Patient 2 had relatively mild CIP, but the effects of other variables are also possible, such as age and exercise tolerance before LDLT.

Previous reports have demonstrated reduced functional status in patients before LT [20], and an association between lower functional status before LT and higher post-transplant mortality [21]. These findings together with our experience of post-LT rehabilitation discussed above suggest that identifying the causes of decreased exercise tolerance before and after LT and planning effective rehabilitative interventions at appropriate timing may improve survival and functional outcome after LT.

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