Peritransplant Gastrointestinal Symptoms in Familial Amyloidotic Polyneuropathy

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Abstract

Objectives: Gastrointestinal dysfunction is a common complication in familial amyloidotic polyneuropathy, and gastrointestinal symptoms are associated with a patient’s nutritional status. The object of this study was to evaluate changes in peritransplant gastrointestinal symptoms and the nutritional status of familial amyloidotic polyneuropathy patients using the modified body mass index following a living-donor liver transplant.

Materials and Methods: In a retrospective analysis, we compared 17 Japanese familial amyloidotic polyneuropathy patients who underwent living-donor liver transplant in Kumamoto University Hospital between 2000 and 2009 with a control group of 28 patients with chronic liver disease. We analyzed the peritransplant gastrointestinal symptoms, nutritional status, duration of central venous catheterization, and postoperative hospital stay. The Mann-Whitney U test and Fisher exact test were used to analyze relations between the familial amyloidotic polyneuropathy group and control group, and the Wilcoxon signed-rank test, to analyze the relation of perioperative modified body mass index, with a value for \( P < .05 \) considered statistically significant.

Results: The duration of central venous catheterization and postoperative hospital stay were significantly longer in the familial amyloidotic polyneuropathy group than they were in the control group. There was no significant difference between modified body mass index preoperatively and 1 year after living-donor liver transplant. Although gastrointestinal symptoms were typically mild before living-donor liver transplant, the familial amyloidotic polyneuropathy group experienced a temporary deterioration in gastrointestinal symptoms after receiving the living-donor liver transplant but recovered after approximately 2 months.

Conclusions: Although familial amyloidotic polyneuropathy patients experienced temporary exacerbations of gastrointestinal symptoms, their nutritional status was not affected during the peritransplant period, and they generally recovered within 2 months.

Key words: Familial amyloidotic polyneuropathy, Liver transplant, Gastrointestinal symptom

Introduction

Familial amyloidotic polyneuropathy (FAP) is a hereditary amyloidosis caused by mutated transthyretin (TTR) and inherited in an autosomal dominant fashion.1,2 Familial amyloidotic polyneuropathy patients have systemic depositions of amyloid fibrils in various organs, often including the gastrointestinal tract. The disease is characterized by sensory-dominant peripheral neuropathy, as well as symptoms in the gastrointestinal tract, heart, eyes, kidneys, and autonomic nervous system.1,3-5

Gastrointestinal dysfunction is a common complication.6,7 More than 90 amyloidogenic TTR (ATTR) variants leading to FAP, of which the Val30Met mutation is the most common.8 The liver synthesizes...
more than 90% of serum TTR, with the remaining produced by the retinal pigment epithelium, choroid plexus, and alpha cells of the pancreas. Therefore, liver transplant (LT) has been used to reduce the progression of FAP, and it is widely accepted that LT may be the only life-saving therapy for FAP patients. Although management of gastrointestinal symptoms and nutritional status are important when treating FAP, there is no report that investigates peritransplant gastrointestinal changes. The aim of this study was to evaluate peritransplant gastrointestinal symptoms and the nutritional status of FAP patients after receiving a living-donor liver transplant (LDLT).

**Materials and Methods**

We performed a retrospective analysis of 17 Japanese FAP patients who underwent an LDLT in Kumamoto University Hospital between 2000 and 2009 with at least 1 year of follow-up. A group of 28 patients (20 patients with hepatitis C virus and 8 patients with hepatitis B virus with or without hepatocellular carcinoma) served as controls, with their chronic liver disease score graded at Child-Pugh class A (3 patients) and class B (25 patients). They underwent an LT during the same time. One patient who had enteral feeding tubes and another patient who underwent retransplant were excluded. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

The diagnosis of FAP was made based on clinical symptoms, histologic amyloid deposition, and genetic testing. Genetic mutations consisted of ATTR Val30Met (n=13, 76.5%), ATTR Tyr114Cys (n=2, 11.8%), ATTR Ser50Ile (n=1, 5.88%), and ATTR Phe33Val (n=1, 5.88%) mutations. The mean duration of the disease before the LDLT was 2.8 ± 1.57 years (range, 0.7-5 y).

The gastrointestinal symptom rating scale was simplified to evaluate changes in gastrointestinal symptoms before and after LDLT (Table 1). We evaluated gastrointestinal symptoms on a 3-point scale for a week until discharge. The nutritional status was evaluated using a modified body mass index (mBMI) value, the product of body mass index (kg/m²), and serum albumin (g/L) to account for edema. Data collected included pre-, peri-, and postoperative factors such as graft size expressed as the ratio of the graft weight to the recipient’s body weight, estimated intraoperative blood loss, duration of central venous catheterization, and postoperative hospital stay.

The Mann-Whitney U test and Fisher exact test were used to analyze relations between the FAP group and the control group. The Wilcoxon signed-rank test was used to analyze the relation of perioperative mBMI. The Friedman test was used to analyze relations in mean modified gastrointestinal symptom rating scale and weeks after LDLT. A value for \( P < .05 \) was considered statistically significant.

**Operative procedure**

**Donor**

Preoperative 3-dimensional computed tomographic cholangiography and intraoperative cholangiography were used to evaluate the donor biliary tree. Hepatic resection was performed without occluding the blood flow. An ultrasonic dissector was used for parenchymal transection. University of Wisconsin solution (ViaSpan; Bristol-Myers Squibb Co.,

| Table 1. The Modified Gastrointestinal Symptom Rating Scale |
|-----------------|----------------|----------------|
| **Score**       | **1 (Mild)**   | **2 (Moderate)** | **3 (Severe)** |
| Frequency of defecation | Increased passage of stools | 1-3 times/d | 3-6 times/d | 6 times/d or more frequently |
|                  | Decreased passage of stools | 1 time/1-3 d | 1 time/3-6 d | 1 time/7 d or less frequently |
| Stool form       | Loose stools   | Slightly loose  | Runny        | Watery        |
|                  | Hard Stools    | Slightly hard  | Hard         | Hard and fragmented |
| Abdominal pains  | Occasional aches and pains | Prolonged and troublesome aches and pains | Severe or crippling pains |
| Nausea and vomiting | Occasional episodes of short duration | Frequent and prolonged nausea, no vomiting | Continuous nausea, frequent vomiting |
New York, NY, USA) or histidine-tryptophan-ketoglutarate solution (CUSTODIOL; Odyssey Pharmaceuticals, Inc., East Hanover, Germany) was used for graft perfusion. Graft selection was based on the body weight of the recipients.

**Recipient**

After a total hepatectomy, the graft was carefully inserted and vascular reconstruction was performed. The graft then was reperfused before proceeding with an anastomosis of the hepatic artery via microsurgery. The biliary tract was reconstructed via duct-to-duct choledochoccholedochostomy in most cases and hepaticojejunostomy in 1 case. The external stent tube (4- or 5-French pancreatic duct tube; Sumitomo Bakelite Co. Ltd., Tokyo, Japan) was placed through the anastomosis site and maintained in situ for at least 3 months.

All patients were prescribed standard immunosuppression with tacrolimus and corticosteroids, with or without mycophenolate mofetil. Steroid treatment was initiated with an injection of 10 mg/kg of methylprednisolone before graft reperfusion during surgery. Steroids were discontinued 3 to 6 months after the transplant.

**Results**

Pre-, peri-, and postoperative factors of the FAP and control groups are shown in Table 2. The FAP group was significantly younger than the control group was (39.1 ± 10.3 y vs 55.2 ± 8.7 y; *P* < .0001) and consisted of more women (58.8% vs 10.7%; *P* = .0015). The duration of surgery was significantly shorter in the FAP group than it was in the control group, but there was less intraoperative blood loss. In addition, the duration of central venous catheterization and postoperative hospital stay were significantly longer in the FAP group than they were in the control group. However, there was no significant differences between the 2 groups regarding graft type, ABO incompatibility, biliary reconstruction methods, and relaparotomies.

Three patients in the control group had complications of by diabetes mellitus (DM) at the time of the LDLT. Although patients with DM may have diabetic autonomic neuropathy and experience gastrointestinal complications, the duration of central venous catheterization and postoperative hospital stay of the 3 DM patients were not longer when compared with the other patients in the control group.

Changes in the gastrointestinal symptoms are shown in Figure 1. Although gastrointestinal symptoms were typically mild before LDLT, the FAP group experienced a temporary deterioration in gastrointestinal symptoms and the mean increased significantly 4 weeks after the LDLT compared with the value before the LT (*P* < .05). However, the gastrointestinal symptoms recovered after approximately 2 months after the LDLT.

The nutritional status of FAP patients before and after the LDLT according to the modified gastrointestinal symptom rating scale is shown in Figure 2. There was no significant difference between preoperative mBMI before the LDLT and mBMI 1 year after the LDLT (765.3 ± 142.0 kg/m² vs 735.7 ± 121.8 kg/m²; *P* = .4932).

**Discussion**

We found that the gastrointestinal symptoms of FAP patients deteriorated temporarily after an LDLT,
which may contribute to the increased duration of central venous catheterization and postoperative hospital stay. However, FAP patients recovered after 2 months, and their nutritional status was not affected by LDLT.

Gastrointestinal tract motility is temporarily impaired after laparotomy. It has been reported that after laparotomy, small bowel activity recovered in 38% of patients by 4 to 8 hours and in 74% patients by 24 hours; additionally, they regained gastric motility within 24 hours and colonic motility in 3 to 5 days.16,17 In FAP, gastrointestinal dysfunction is a common complication generally attributed to autonomic neuropathy,6,18 and the gastrointestinal symptoms may take longer to alleviate in these patients. However, there is no study that specifically examines the recovery of FAP patients after a laparotomy.

Furthermore, relaparotomy and/or hepatico-jejunostomy with a Roux-en-Y limb may exacerbate gastrointestinal symptoms.19 However, no significant difference was found between relaparotomy, biliary reconstruction methods, and gastrointestinal symptoms. Patients with DM also may have autonomic neuropathy. Therefore, patients with DM from the control group were compared with the FAP patients, although the DM patients did not experience the same gastrointestinal symptoms as the FAP patients did. This result may be due to the small number of DM patients in the control group and/or fewer gastrointestinal symptoms experienced by these patients. Our study did not include tests of autonomic function and gastrointestinal motility, such as electrogastrography. Further research is required to clarify the role of autonomic neuropathy.

During surgery, we took careful note of the total clamping time of the portal vein in patients without liver cirrhosis. However, it is likely that FAP patients without portal hypertension had not developed collateral blood circulation, in contrast to patients with chronic liver disease in the control group. Although we did not have operative findings demonstrating bowel congestion, it is possible that bowel congestion owing to the total clamping of the portal vein was more severe in the FAP group.

In conclusion, recovery of gastrointestinal function takes longer after an LDLT in FAP patients. Therefore, we need to carefully manage the postoperative nutrition in these patients including total parenteral nutrition and tube feeding.

References