

Impact of Liver Transplantation on Transthyretin-Related Ocular Amyloidosis in Japanese Patients

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Objective: To evaluate the long-term impact of liver transplantation on ocular manifestations of familial amyloid polyneuropathy (FAP) in Japanese patients.

Methods: Medical records were retrospectively reviewed in a long-term follow-up study. Of 52 patients with FAP amyloidogenic transthyretin Val30Met, 22 patients underwent liver transplantation. We assessed ocular manifestations, including amyloid deposition at the pupillary border, pupillary border with irregularity, vitreous opacities, and glaucoma, in patients who underwent liver transplantation. In addition, we compared the clinical characteristics of vitreous opacities—the most common ocular manifestation of FAP—in patients who underwent liver transplantation and those who did not to determine the effect of transplantation on the progression of ocular amyloidosis.

Results: Mean time after FAP onset was 10 years and after liver transplantation was 7 years in patients who underwent liver transplantation. All ocular manifestations increased with time after transplantation. Eight patients (36%) developed vitreous opacities and 4 patients (18%) developed glaucoma during follow-up. Mean time from FAP onset to vitreous opacities onset was significantly shorter in patients with early-onset disease who underwent liver transplantation than in those who did not.

Conclusions: Patients with FAP who undergo liver transplantation continue to have a long-term risk of severe ocular manifestations, especially vitreous opacities and glaucoma, which can restrict their daily lives, even after liver transplantation.

Arch Ophthalmol. 2010;128(2):206-210

TRANSTHYRETIN-RELATED familial amyloid polyneuropathy (FAP), a fatal hereditary amyloidosis, is characterized by systemic accumulation of mutant amyloidogenic transthyretin (ATTR) in peripheral nerves and several organs.^{1,2} Liver transplantation has been believed to be a promising method for halting the progression of neurologic complications in patients with transthyretin-related FAP inasmuch as the liver is the primary synthetic source of ATTR found in serum.^{3,4} However, ocular complications have reportedly continued and worsened even after liver transplantation^{5,6} because ocular tissues, mainly retinal pigment epithelium (RPE), also synthesized ATTR.^{7,8} Detection of a significant amount of ATTR in aqueous humor and vitreous from patients with FAP after liver transplantation has previously been reported.^{9,10}

Among the hereditary systemic amyloidoses, FAP ATTR Val30Met is the most common.^{1,2} Moreover, ocular manifestations, such as abnormal conjunctival vessels, dry eye, amyloid deposition at the pu-

pillary border and on the lens surface, pupillary border with irregularity, vitreous opacities, and glaucoma, are common in patients with FAP ATTR Val30Met, and the occurrence of these involvements increases with time.¹¹⁻¹⁴ Early-onset disease (before age 50 years) is fatal, with an expected survival of approximately 10 years from onset of the disease for Japanese patients.^{1,2} Because most Japanese patients with FAP have early-onset disease, long-term follow-up of ocular manifestations could not be fully evaluated before the introduction of liver transplantation.

In the Kumamoto district, since 1994, patients with FAP have undergone liver transplantation. Consequently, their survival has improved significantly,^{4,15} so long-term follow-up of ocular involvements has become feasible. However, the effects of liver transplantation on the progression of ocular manifestations of FAP have not, in fact, been thoroughly elucidated. The aim of this study is, therefore, to evaluate the long-term impact of liver transplantation on ocular involvements in Japanese patients with FAP ATTR Val30Met.

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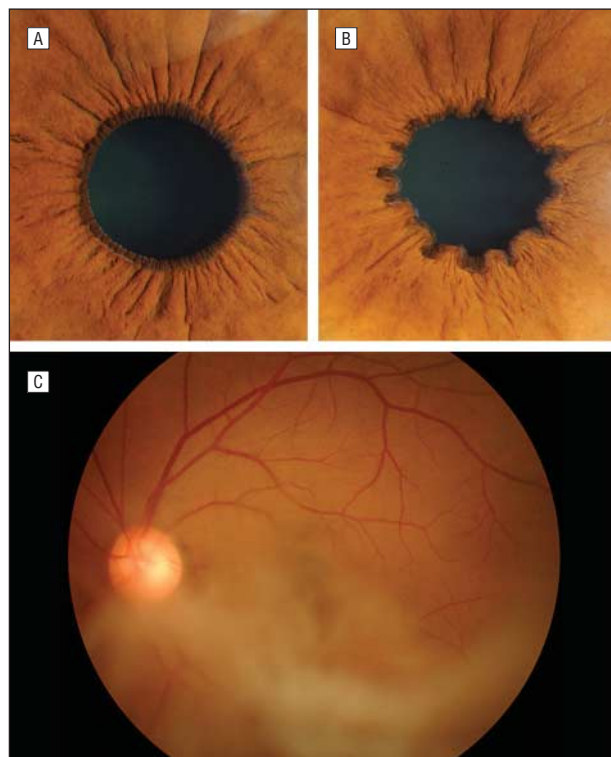


Figure 1. Ocular manifestations in transthyretin-related familial amyloid polyneuropathy. A, Amyloid deposition at the pupillary border. B, Pupillary border with irregularity. C, Vitreous opacities.

METHODS

PATIENTS

This retrospective analysis studied 52 patients with FAP ATTR Val30Met who had visited the Department of Ophthalmology, Kumamoto University Hospital, between November 19, 1987, and December 15, 2008. All the patients were initially evaluated for clinical signs of FAP and later had a definitive diagnosis of FAP on the basis of amyloid deposition in biopsy samples and results of genetic investigations. Of these 52 patients, 22 underwent liver transplantation.

DATA COLLECTION

We obtained clinical data from medical records. For patients who underwent liver transplantation, we evaluated development of the following ocular manifestations: amyloid deposition at the pupillary border (**Figure 1A**), pupillary border with irregularity (**Figure 1B**), vitreous opacities (**Figure 1C**), and glaucoma. Age at the onset of FAP was defined as the age at which the patient first reported typical symptoms, such as polyneuropathy, autonomic dysfunction, and visual disturbance. The presence of vitreous opacities was determined with the aid of mydriatic fundus examinations. Vitreous opacities were classified into 3 categories—mild, moderate, and severe—according to the classification given in a previous study.¹³ The onset of glaucoma was defined as an elevated intraocular pressure value (≥ 21 mm Hg), changes in the optic nerve head appearance, and glaucomatous changes in visual fields. Amyloid deposition on the lens surface was excluded in this study because cataract surgery may have confounded evaluation of the development of amyloid deposition during follow-up. In addition, we investigated the occurrence of vitreous opacities in patients who did not undergo liver transplantation. To evalu-

Table 1. Clinical Data for Patients With FAP ATTR Val30Met Who Underwent Liver Transplantation

Characteristic	Value
Sex, M/F, No.	10/12
Age at onset of FAP, mean (range), y	33 (24-54)
Early onset/late onset	
Patients, No.	21/1
Age, mean (range), y	32 (24-46)/54 (54)
Age at liver transplantation, mean (range), y	36 (24-58)
Time from onset of FAP to liver transplantation, mean (range), y	2.6 (0.7-5.0)
Time after liver transplantation, mean (range), y	7.2 (1.2-13.7)
Duration of FAP after onset, mean (range), y	9.8 (3.2-17.7)

Abbreviations: ATTR, amyloidogenic transthyretin; FAP, familial amyloid polyneuropathy.

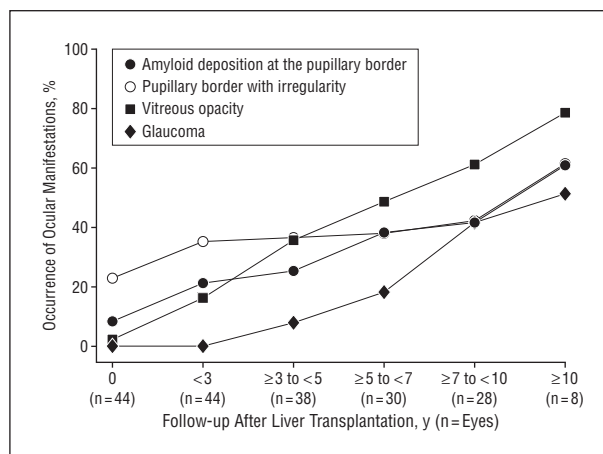


Figure 2. Changes in the occurrence of ocular manifestations in transthyretin-related familial amyloid polyneuropathy. Occurrence of all the ocular manifestations increased with time after liver transplantation.

ate whether liver transplantation had any effects on the development of ocular amyloidosis, we compared the clinical characteristics of vitreous opacities—the classic sign of ocular amyloidosis—in patients who underwent (with) vs those who did not undergo (without) liver transplantation.

DATA ANALYSIS

Differences in continuous and categorical variables were compared using the Mann-Whitney test and the Fisher exact test, respectively. Visual acuity was measured via standard Landolt C charts, and values were converted to letter scores on the Early Treatment Diabetic Retinopathy Study chart.

RESULTS

DEVELOPMENT OF OCULAR MANIFESTATIONS AFTER TRANSPLANTATION

Table 1 presents clinical data for patients with FAP ATTR Val30Met who underwent liver transplantation. All the patients except 1 had early-onset disease; and mean time after liver transplantation was approximately 7 years, and mean duration of FAP after onset was approximately 10 years. All ocular manifestations in patients with FAP increased after transplantation (**Figure 2**). Vitreous opaci-

Table 2. Clinical Data for 15 Patients With FAP ATTR Val30Met Who Had Progressive or Nonprogressive Ocular Manifestations 5 Years After Liver Transplantation

	Ocular Manifestations		P Value
	Progressive (n=10)	Nonprogressive (n=5)	
Sex, M/F, No.	6/4	1/4	.28
Age at onset of FAP, mean (range), y	36 (28-54)	31 (26-35)	.50
Age at liver transplantation, mean (range), y	39 (30-59)	33 (29-36)	.39
Time from onset of FAP to follow-up year 5, mean (range), y	8.0 (6-10)	6.4 (6-8)	.02

Abbreviations: ATTR, amyloidogenic transthyretin; FAP, familial amyloid polyneuropathy.

Table 3. Clinical Data for 14 Patients With FAP ATTR Val30Met Who Had Vitreous Opacities With or Without Undergoing Liver Transplantation

	Transplantation Patients (n=7)	No-Transplantation Patients (n=7)	P Value
All patients			
Sex, M/F, No.	4/3	2/5	.59
Age at onset of FAP, mean (range), y	39 (28-54)	53 (36-73)	.04
Age at onset of VOs, mean (range), y	44 (32-60)	57 (46-73)	.02
Time from onset of FAP to VOs, mean (range), y	5.0 (0-9)	4.7 (0-11)	.80
Patients with early-onset disease, No.	6	3	.27
Age at onset of FAP, mean (range), y	37 (28-46)	42 (36-47)	.32
Age at onset of VOs, mean (range), y	42 (32-51)	52 (46-56)	.05
Time from onset of FAP to VOs, mean (range), y	4.7 (0-8)	9.7 (8-11)	.03
Degree of VOs, No. (%)			
Mild	3 (50)	3 (100)	
Moderate	2 (33)	0 (0)	
Severe	1 (17)	0 (0)	
Vitreous surgery, No. (%)	3 (50)	0 (0)	.46
Visual acuity, letters, mean (range)			
At first visit	89 (85-94)	86 (80-94)	.19
At last visit	80 (15-94)	68 (30-89)	.17

Abbreviations: ATTR, amyloidogenic transthyretin; FAP, familial amyloid polyneuropathy; VOs, vitreous opacities.

ties and glaucoma were confirmed in 2.3% and 0% of patients, respectively, at the time of liver transplantation, and in 80% and 50% of patients, respectively, 10 years after transplantation. Amyloid deposition at the pupillary border and pupillary border with irregularity seemed to develop before vitreous opacities and glaucoma. Cotton wool–like vitreous opacities developed in 11 eyes of 8 patients during follow-up. Five of these eyes required vitreous surgery after liver transplantation. Glaucoma developed in 6 eyes of 4 patients. Four of these eyes needed filtering surgery after liver transplantation.

Fifteen patients were followed up for a minimum of 5 years after liver transplantation. Of these 15 patients, 10 showed progression of any ocular involvement at 5 years (**Table 2**). Five years after liver transplantation, time from onset of FAP was significantly longer in the group with progressive ocular manifestations than that in the group with nonprogressive manifestations.

COMPARISON OF VITREOUS OPACITIES IN PATIENTS WITH VS WITHOUT TRANSPLANTATION

To evaluate whether liver transplantation had positive effects on the development of ocular amyloidosis, we com-

pared the clinical characteristics of vitreous opacities in 2 groups of patients with FAP ATTR Val30Met: those with and those without a liver transplant (**Table 3**). Patients who did not undergo transplantation were significantly older at the onset of FAP and the start of vitreous opacities than were patients who did undergo this treatment. No significant difference in the time from onset of FAP was found between groups. Furthermore, we compared both groups for the development of vitreous opacities as related to early-onset disease, which is the type of disease in most Japanese patients with FAP. Time from the onset of FAP to the onset of vitreous opacities in patients who underwent liver transplantation was significantly shorter than that for patients who did not undergo transplantation. Moderate or severe vitreous opacities were more commonly observed in patients who underwent transplantation than in those who did not and in several patients who underwent vitrectomy. Although some patients underwent vitrectomy because of decreased visual acuity due to the development of vitreous opacities, visual acuity improved promptly after surgery. Thus, visual acuity in most patients has been maintained, although vitreous surgery was needed in some cases; however, visual acuity significantly decreased in 1 patient in each group because of the progression of glaucoma.

It is widely accepted that liver transplantation can halt the progression of systemic clinical symptoms of FAP.^{3,4} However, several studies^{5,6,9,10} from clinical and laboratory settings have suggested that patients with FAP who undergo liver transplantations are still at risk for ocular involvements because of the ocular synthesis of transthyretin. In this study, long-term follow-up results showed a clear increase in the occurrence of all ocular manifestations with time, even after liver transplantation.

We previously reported the clinical characteristics of ocular manifestations in patients with FAP ATTR Val30Met, almost all of whom had not undergone liver transplantation (a few had undergone transplantation within a year), and who had a mean time from the onset of FAP of approximately 4 years.¹² In contrast, the present study evaluated ocular disorders of patients who had undergone liver transplantation, with the mean time after the onset of FAP being approximately 10 years and the mean time after transplantation being approximately 7 years. In a previous study,¹² vitreous opacities and glaucoma each occurred in only 2 of 37 patients (5.4%); in the present study, however, 8 patients (36%) had vitreous opacities and 4 (18%) had glaucoma during follow-up. Furthermore, time from FAP onset was the most important predictive factor for whether ocular involvements were observed 5 years after liver transplantation. Many more patients will probably develop severe ocular manifestations across time.

Sandgren et al¹⁶ recently reported postoperative ocular involvements in Swedish liver transplant recipients with FAP ATTR Val30Met. It is well known that Swedish patients have different phenotypes compared with patients in Japan; most Swedish patients have late-onset disease, with a far better prognosis regarding severity of symptoms and survival.^{2,17} In their study of 48 Swedish patients who had undergone liver transplantation, the mean age at the onset of FAP was 42 years and the mean age at liver transplantation was 46 years. Follow-up after liver transplantation was 40 months in patients without ocular involvements and 69 months in patients with ocular involvements; 13% of patients developed vitreous opacities, and 8% developed glaucoma. The occurrence of vitreous opacities and glaucoma in our results seems to be higher than that in the Swedish study. Although other unknown factors may affect these results, the likely reasons are the younger age at onset and the longer follow-up in this study compared with the Swedish study.

We previously demonstrated in rabbit eyes that transthyretin is synthesized not only in the RPE but also in the ciliary pigment epithelium.⁸ The present findings showed that amyloid deposition at the pupillary border and the pupillary border with irregularity seemed to occur earlier than vitreous opacities; Sandgren et al¹⁶ obtained the same results. These findings support the previous suggestion that the origin of the amyloid deposited in the anterior segment could be the ciliary pigment epithelium rather than the RPE.

In the eyes of patients who had not undergone liver transplantation, the sources of the amyloid deposited in

ocular tissues are the RPE and ciliary pigment epithelium and the liver via the systemic circulation. A difference in the origin of amyloid may lead to the development of ocular disorders in patients with FAP whether or not they undergo liver transplantation. Thus, we compared the development of vitreous opacities, the most common ocular involvement of FAP, in patients with and without transplantation. Furthermore, because early- and late-onset cases have different clinical characteristics, and all patients who underwent liver transplantation except 1 had early-onset disease, we evaluated vitreous opacities in early-onset cases. Vitreous opacities developed significantly more rapidly in patients who underwent transplantation than in those who did not. In addition, all patients without a liver transplant had mild vitreous opacities; none had moderate or severe opacities. In contrast, half of the patients who underwent transplantation had moderate or severe vitreous opacities. Because of the small sample, this finding is difficult to explain fully. It has been suggested that patients with potentially progressive vitreous opacities who did not undergo transplantation might not have survived long enough to develop vitreous amyloidosis. Patients with FAP ATTR Val30Met exhibit a wide spectrum of clinical phenotypes regarding characteristics such as age at the onset of FAP, disease progression, and penetrance, even when their diseases result from the same mutation, as seen in most autosomal dominant disorders.^{2,17} Several studies¹⁸⁻²⁰ of the phenotype-genotype association of FAP have suggested that although the Val30Met mutation is required for the disease, additional genetic factors function to control the diversity of clinical expression. Little information about the relationship between ocular involvements and transthyretin gene polymorphisms exists, but an evaluation of this relationship is needed for understanding ocular amyloid formation. In any case, that the time from the onset of FAP to the occurrence of vitreous opacities may be shorter than expected is important information for patients undergoing liver transplantation.

In conclusion, most patients with FAP undergoing liver transplantation will probably develop severe ocular manifestations, especially vitreous opacities and glaucoma, which can restrict their daily lives. To maintain a good quality of life, precise, long-term evaluation and development of new therapeutic strategies are needed. The present long-term follow-up results, which were made possible by the introduction of liver transplantation, may be extremely valuable and provide important information for evaluation of the progression of transthyretin-related ocular amyloidosis.

Submitted for Publication: June 29, 2009; final revision received September 22, 2009; accepted September 24, 2009.

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Author Contributions: Dr Kawaji had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (Dr Tanihara).

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