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［Ⅳ］研究成果の刊行物・別刷

RESEARCH PAPER

Changes in pathological and biochemical findings of systemic tissue sites in familial amyloid polyneuropathy more than 10 years after liver transplantation

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ABSTRACT

Objective To elucidate the long-term effects of liver transplantation (LT) on familial amyloid polyneuropathy (FAP).

Methods We investigated clinicopathological and biochemical characteristics of systemic tissues in four autopsied cases of FAP patients surviving more than 10 years after LT and seven autopsied cases without LT. For analysing the truncated form of transthyretin (TTR) in amyloid, we also employed specimens from additional 18 FAP patients.

Results Several tissue sites such as the heart, tongue and spinal cord had moderate-to-severe amyloid deposits but other tissues showed no or mild amyloid deposition. Those findings seemed similar to those observed in senile systemic amyloidosis (SSA), a sporadic amyloidosis caused by wild-type (WT) TTR. Also, amyloid deposits in systemic tissue sites except for the spinal cord in patients after LT derived mostly from WT TTR secreted from the normal liver grafts. In addition, in non-transplantation patients, proportions of WT TTR seemed to be relatively high in those tissue sites in which patients after LT had severe amyloid deposition, which suggests that WT TTR tends to form amyloid in those tissue sites. Finally, although the truncation of TTR in amyloid deposits did not depend on undergoing LT, we elucidated the truncation of TTR occurred predominantly in patients from non-endemic areas of Japan, where FAP amyloidogenic TTR V30M patients are late onset and low penetrance, compared with patients from an endemic area of Japan.

Conclusions FAP may shift to systemic WT TTR amyloid formation after LT, which seems to be similar to the process in SSA. The truncation of TTR in amyloid deposits may depend on some genetic or environmental factors other than undergoing LT.

INTRODUCTION

Familial amyloid polyneuropathy (FAP) is an autosomal dominant form of fatal hereditary systemic amyloidosis, whose most common cause is mutant (MT) transthyretin (TTR).[1 2] TTR is a plasma protein synthesised mainly in the liver and in the choroid plexus of the brain and retinal pigment epithelial cells; as a homotetramer composed of 127-residue monomeric subunits, it serves as a transport molecule for thyroxine and retinol-binding protein, circulates in blood and cerebrospinal fluid and occurs in aqueous humour. To date, more than 120 TTR mutations have been identified, most of which result in the development of FAP.[2] Sensorimotor polyneuropathy, autonomic dysfunction, cardiac and renal failure and gastrointestinal (GI) tract disorders, all of which may lead to death usually within 10 years, have been documented in patients with FAP caused by amyloidogenic TTR (ATTR) V30M, which is the most common FAP genotype in the world.[1] Phenotypic differences among patients with the same ATTR V30M mutation are well known and depend on geographic area. Families originating from Portugal and two endemic areas in Japan (Arao City in Kumamoto Prefecture and Ogawa Village in Nagano Prefecture) usually have early-onset disease and high penetrance, whereas other Japanese kindred and Swedish families evidence late-onset disease and low penetrance.[3 4]

Since 1990, FAP patients have undergone liver transplantation (LT) as treatment for the disease.[5] According to data in the FAP World Transplant Registry (http://www.fapwtr.org), approximately 120 LTs have been performed annually for FAP throughout the world. Replacement of diseased livers of FAP patients with healthy livers causes WT TTR to replace MT TTR in the body, except for the cerebrospinal fluid and the eyes, which contain MT TTR secreted by the choroid plexus and the retina, respectively, even after LT.[6 7] LT reportedly prolonged survival of FAP ATTR V30M patients who had been carefully selected for transplantation.[8 9] However, recent studies suggest that LT failed to prevent progression of cardiac amyloidosis in FAP ATTR V30M patients after LT,[5 10] because of continued formation of amyloid derived mainly from WT TTR secreted from the normal liver graft.[11 12] To understand the specific effects of LT on FAP, we must know why and how the disease progresses in systemic tissue sites even after LT, but these issues are still poorly understood.

In the present study, we investigated clinical, histopathological and biochemical characteristics of

systemic tissue samples obtained from FAP ATTR V30M patients surviving more than 10 years after LT and compared them with those from non-LT FAP ATTR V30M patients. We also verified the hypothesis that certain pathological relationships exist between FAP long after LT and senile systemic amyloidosis (SSA), a sporadic systemic amyloidosis formed by WT TTR which is partially truncated.[13 14] We believe that this information will help understanding of the long-term effects of LT on FAP. In addition, we also indicated factors involved in the truncation of TTR in amyloid deposits of FAP ATTR V30M patients.

PATIENTS AND METHODS

Patients

Between 1990 and 2011, 80 patients with FAP ATTR V30M visited Kumamoto University Hospital, and 37 of these patients underwent LT. In this study, we evaluated four autopsied FAP ATTR V30M patients who had survived more than 10 years after LT. The other 33 patients who had undergone LT were still living. Our criteria for performing LT for FAP patients were as follows: age younger than 60 years, duration of disease from onset <5 years, creatinine clearance >70 mL/min, modified body mass index >600, no cardiomegaly, ambulatory without help and neuropathy limited to the lower limbs.[15] We also studied seven non-LT FAP ATTR V30M patients who were autopsied at Kumamoto University Hospital between 1990 and 2011. All patients in this study were heterozygous for the ATTR V30M mutation. Table 1 provides detailed clinical information about the study patients. We used the FAP clinical score to assess clinical symptoms.[16] We previously reported details of cases LT1[17] and LT3.[18] For analysing the truncated form of TTR in amyloid, we also employed formalin-fixed autopsy or biopsy specimens from additional 18 FAP patients with heterozygous for the ATTR V30M (see online supplementary table S1).

Congo red staining and the degree of amyloid deposition

Formalin-fixed tissue samples were embedded in paraffin, serially sectioned at a thickness of 4 μm and placed on microscope slides. Slides were stained with haematoxylin-eosin and alkaline Congo red; they were also examined under polarised light to detect the presence of green birefringence. The degree of amyloid deposition was determined according to a previous study with some modifications.[19] Online supplementary table S2 provides detailed information about the scoring of amyloid deposits at each tissue site.

Extraction of amyloid proteins

Amyloid proteins were extracted from frozen tissue specimens according to the methods of Kaplan *et al*[20] with some modifications. In brief, soluble components were removed from specimens (100 mg wet weight) by homogenising the tissues in 10 mL of cold phosphate-buffered saline (PBS) by using a glass-Teflon homogeniser (AS ONE Co., Osaka, Japan), followed by centrifugation at 14 000 g for 10 min at 4°C. The protein concentration in the PBS washes was monitored by measuring optical density A280. This homogenisation–centrifugation process was repeated until the A280 value of the supernatant was below 0.2 (usually 10–15 times). The resulting pellets were

Table 1 Clinical characteristics of FAP ATTR V30M patients

Characteristic	LT1*	LT2	LT3†	LT4	NL1	NL2	NL3	NL4	NL5	NL6	NL7
Family line	E	E	E	N	E	E	E	E	N	E	E
Sex	M	M	F	M	M	M	F	F	M	M	F
Age at FAP onset (years)	26	27	40	47	22	23	27	34	56	60	63
Age at LT (years)	29	28	47	49	NA	NA	NA	NA	NA	NA	NA
Age at death (years)	42	44	57	59	34	38	42	43	63	67	69
Time from FAP onset to LT (years)	2.5	0.6	7.1	2.2	NA	NA	NA	NA	NA	NA	NA
Time from LT to death (years)	13	16	10	10	NA	NA	NA	NA	NA	NA	NA
Time from FAP onset to death (years)	16	17	17	12	12	15	14	9	8	7	6
Concurrent disorders	AI, HK	Rej	UM	None	None	None	None	None	None	None	OT
Reasons for not performing LT‡	NA	NA	NA	NA	MC	MC	MC	MC	Nam, CM	AA, CM, RF, Nam	AA, Nam
FAP clinical score§ at the end stage of disease											
Sensory abnormalities	5	7	4	10	16	20	22	22	21	16	20
Motor function	0	0	0	13	16	17	20	18	19	13	11
Autonomic disorders	6	16	2	16	18	22	22	19	8	18	16
Visceral organ impairment	12	12	12	16	20	20	20	24	16	24	20
Time from FAP onset to determination of FAP clinical score (years)	14.7	15.8	14.7	10.4	11.3	14.5	13.5	9	6.9	7	6
Heart weight (g) at autopsy	430	510	340	1044	490	390	320	NE	560	438	240
Main causes of death	VF, HK¶	HF**	CF	CF	CF, NS	SD, CF, NS	SD, CF, NS	CF, RF	CF	CF, RF	CF, NS, Pne

*We previously reported detailed clinical findings of the case LT1.[17]
†We also previously reported detailed clinical findings of the case LT3.[18]
‡We describe our criteria for LT in Materials and Methods.
§We used the FAP clinical score to assess clinical symptoms.[16]
¶Alcoholism probably caused hypokalaemia.
**Chronic graft rejection probably caused hepatic failure.
AA, advanced age at the onset; AI, alcoholism; ATTR, amyloidogenic; CF, cardiac failure; CM, cardiomegaly; E, from an FAP-endemic area of Japan (Arao City of Kumamoto Prefecture); F, female; FAP, familial amyloid polyneuropathy; HF, hepatic failure; HK, hypokalaemia; LT, liver transplantation; LT1–4, patients underwent LT; M, male; MC, match our criteria for LT, but patients did not undergo LT because they decided not to do so or because of a shortage of liver grafts; N, from an FAP-non-endemic area of Japan; NA, not applicable; Nam, non-ambulatory without help; NE, not examined; NK, not known; NL1–7, non-LT patients; NS, nephrotic syndrome; OT, old pulmonary tuberculosis; Pne, pneumonia; Rej, rejection of the liver graft; RF, renal failure; SD, sudden death; SL, shortage of liver grafts; UM, uterine myoma; VF, ventricular fibrillation.

suspended in 1 mL of 20% acetonitrile containing 0.1% trifluoroacetic acid. The mixture was incubated at room temperature for 5 h with mixing and was then centrifuged again. Supernatants were pooled and lyophilised for use in experiments. On the other hand, to extract amyloid proteins from formalin-fixed, paraffin-embedded specimens, we used the biochemical methods of Layfield *et al.*[21] In brief, isolated tissue pellets incubated at 90°C for 15 min in Laemmli sample buffer (Bio-Rad, Hercules,California, USA) containing 8 M urea were subjected to SDS-PAGE and were then transferred to nitrocellulose membranes for immunoblotting.

In-gel digestion and mass spectrometric analysis

Lyophilised amyloid proteins were dissolved in 50 μL of a sample buffer (Bio-Rad, Hercules, California, USA) and then separated on a 12.5% polyacrylamide gel in a Tris–tricine system. The protein bands were visualised by silver staining. A band at approximately 15 kDa (TTR monomer) was cut from the gels. Trypsin (Promega, Madison, Wisconsin, USA) was used to digest the proteins to obtain the peptides, which were analysed by surface-enhanced laser desorption/ionisation time-of-flight mass spectrometry (Bio-Rad). The spectrum peaks corresponding to tryptic peptides consisting of amino acid residues 22–34, which contained the MT amino acid at position 30, were investigated. The heights of the peaks were measured to give relative indications of quantity.

Detection of the truncated form of TTR

After separation of the extracted amyloid proteins on a 12.5% polyacrylamide gel, samples were transferred to a nitrocellulose membrane (Bio-Rad). Polyclonal antisera against the truncated form of TTR 50–127 (TTR50–127), produced in rabbits, were diluted 1 : 2000 and were used as primary antibodies.[11] A goat anti-rabbit antibody conjugated with horseradish peroxidase (Dako, Glostrup, Denmark), diluted 1 : 5000, was used as a secondary antibody. The reaction was visualised by utilising an enhanced chemiluminescence system (GE Healthcare, Buckinghamshire, UK).

Statistical analysis

Data were evaluated with Student t test or Pearson's χ^2 test. All analyses were performed with JMP V.5.1 (SAS Institute Japan, Tokyo, Japan). p Values of less than 0.05 were regarded as statistically significant.

RESULTS

Clinical and histopathological findings of FAP ATTR V30M patients more than 10 years after LT

As table 1 shows, patients with LT had milder neurological symptoms at the end stage of the disease than patients without LT. Although patients without LT (except for case NL5) manifested nephrotic syndrome or renal failure at the end stage of the disease, patients with LT did not have renal dysfunction (table 1). Three of four patients with LT died of cardiac disorders caused by amyloid deposits, and one transplantation patient (LT2) died of hepatic failure caused by chronic graft rejection.

Microscopic examinations revealed that FAP patients long after LT had smaller amyloid deposits than non-LT patients in peripheral nerves (figure 1A,B, table 2). In the kidney of LT patients, no or only mild amyloid deposition occurred, except for mild-to-moderate deposits in the papilla, but non-LT patients, except for case NL5 originating from an FAP-non-endemic area, showed moderate-to-severe amyloid deposits (figure 1C,D, table 2). Also, in the thyroid gland, LT patients had only mild amyloid deposits (figure 1E), whereas non-LT patients developed severe amyloid deposits (figure 1F). In the GI tract, amyloid deposits were limited primarily to the vascular walls in LT patients (figure 1G), except for case LT4 originating from an FAP-non-endemic area (table 2). Moderate-to-severe amyloid deposits including those in the basal laminae of the GI tract occurred, however, in non-LT patients (figure 1H). We observed severe amyloid deposits, however, in the heart and tongue of patients with and without LT (figure 1I,J, table 2). In addition, we analysed the spinal cord and found moderate-to-severe amyloid deposits in LT patients (figure 1K,L). The amounts of amyloid deposited in the spinal cord differed among non-LT patients (table 2).

Proportion of WT TTR in amyloid deposits in systemic tissue sites

To determine the proportion of WT TTR in the total TTR in amyloid deposits at each tissue site, we detected tryptic peptides TTR22–34, which included position 30, derived from amyloid-forming WT and MT TTR (WT TTR: 1367 Da; MT TTR: 1399 Da) in various tissue sites by means of mass spectrometric analyses (see online supplementary figure S1). Table 3 shows that patients more than 10 years after LT had amyloid deposits derived mainly from WT TTR in systemic tissues except for the spinal cord, in which amyloid-forming TTR derives from the choroid plexus. In non-LT patients, amyloid deposits contained relatively low proportions of WT TTR in the nerves, spinal cord, kidney and thyroid gland but relatively high proportions in the heart, tongue, lung and GI tract (table 3).

Truncation of TTR in amyloid deposits

Immunoblotting with polyclonal antisera against TTR50–127 revealed that systemic amyloid deposits in two patients originating from an FAP-non-endemic area (cases LT4 and NL5) clearly contained the truncated form of TTR, but those in other patients had almost no truncated TTR (figure 2A, and see online supplementary table S3). The presence of truncated TTR depended on neither tissue sites nor the WT TTR proportion of amyloid deposits. Even in the spinal cord, where amyloid deposits consisted mainly of MT TTR (table 3) secreted from the choroid plexus, amyloid deposits clearly contained the truncated TTR in the cases originating from an FAP-non-endemic area (LT4 and NL5) (figure 2B).

To elucidate factors involved in the truncation of TTR in amyloid deposits, we also analysed tissue specimens of 29 FAP ATTR V30M patients including additional 18 FAP patients (see online supplementary table S1). As shown in table 4, the truncation of TTR in amyloid deposits was related to residence, age and sex of patients, but not undergoing LT. Especially, the residence of patients clearly correlated with the truncation of TTR in amyloid deposits. In detail, patients from an endemic area did not have the truncated TTR except for the oldest patient, and all patients from non-endemic areas had the truncated TTR in amyloid deposits (see online supplementary tables S1 and S4).

DISCUSSION

The present case series study provides a comparison of systemic pathological and biochemical findings from autopsy specimens of patients with FAP ATTR V30M who survived more than 10 years after LT and corresponding findings for non-LT patients.

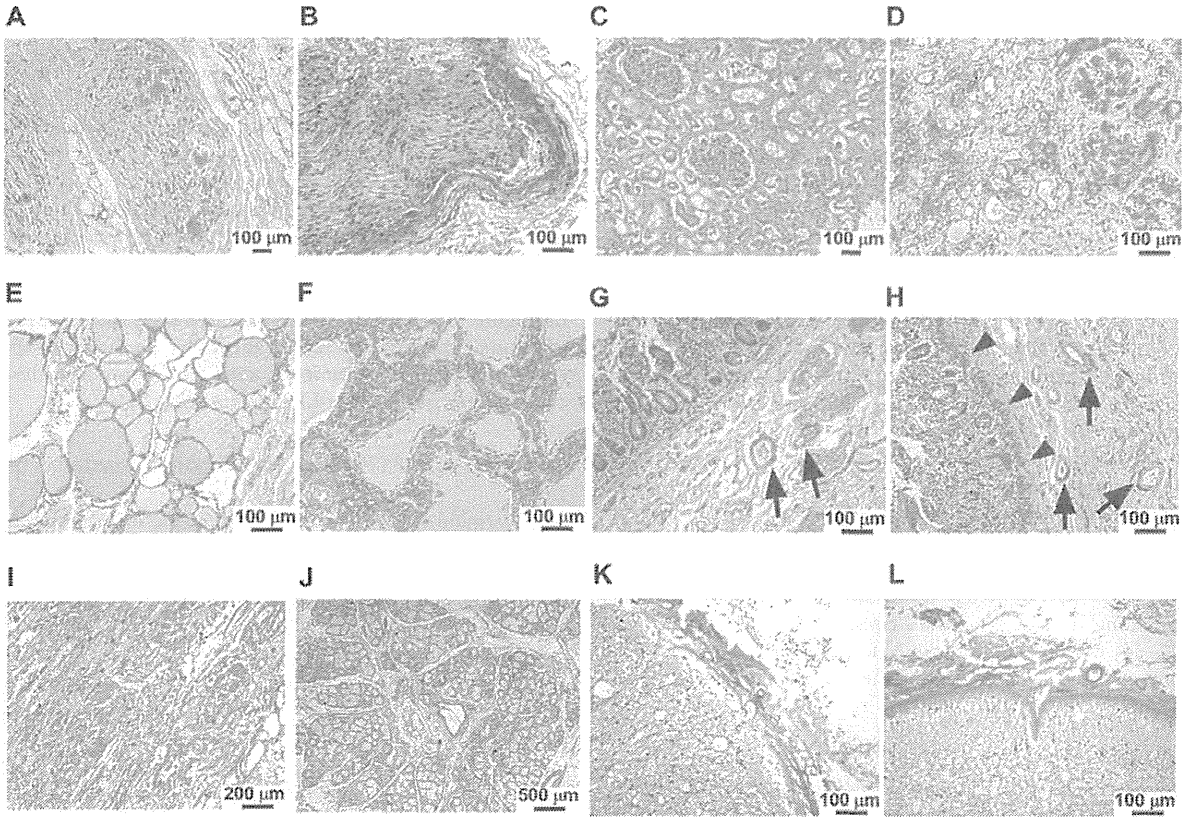

Figure 1 Histopathological findings in familial amyloid polyneuropathy amyloidogenic TTR V30M patients with and without LT. (A, B) The sciatic nerve of a patient after LT (LT4) (A) and a non-LT patient (NL6) (B). (C, D) The kidney of a patient after LT (LT1) (C) and a non-LT patient (NL6) (D). (E, F) The thyroid gland of a patient after LT (LT3) (E) and a non-LT patient (NL2) (F). (G, H) The small intestine of a patient after LT (LT1) (G) and a non-LT patient (NL6) (H). Arrows and arrowheads indicate amyloid deposits in vascular walls and basal laminae, respectively. (I) The heart of a patient after LT (LT4). (J) The tongue of a patient after LT (LT4). (K, L) The spinal cord of a patient after LT (LT3) (K) and a non-LT patient (NL3) (L). (A–L) Congo red staining.

Table 2 Distribution and degree of amyloid deposits in FAP ATTR V30M patients with and without LT

Tissue	LT1	LT2	LT3	LT4	NL1	NL2	NL3	NL4	NL5	NL6	NL7
Peripheral nerve											
Sciatic nerve	2	3	2	2	NE	NE	NE	NE	4	5	4
Sural nerve	0	2	1	0	NE	NE	4	NE	2	NE	NE
Sympathetic nerve	4	3	NE	4	NE	NE	NE	NE	2	NE	NE
Spinal cord	4	5	4	3	v+	4	4	NE	v+	NE	v+
Kidney											
Glomerulus	0	0	1	0	4	4	3	NE	0	4	4
Papilla	2	2	3	2	4	4	4	NE	v+	4	5
Thyroid gland	1	1	2	1	NE	5	4	NE	4	5	NE
GI tract											
Small intestine	v+	v+	v+	4	4	4	2	NE	2	3	4
Large intestine	v+	2	v+	3	4	3	3	NE	3	3	4
Heart	4	4	4	5	4	4	4	4	4	4	4
Tongue											
Small salivary gland	5	5	NE	5	3	4	NE	NE	4	NE	NE
Other sites	3	4	NE	4	2	3	2	NE	5	3	3
Submandibular gland	NE	4	NE	5	NE	NE	NE	NE	5	NE	NE
Lung	2	1	2	4	2	2	2	NE	5	1	3

ATTR, amyloidogenic; FAP, familial amyloid polyneuropathy; GI, gastrointestinal; LT, patients who underwent LT; NE, not examined because of non-availability of formalin-fixed tissue specimens; NL, non-LT patients; v+=amyloid deposits limited to vascular walls; 0=not detected; amyloid deposits in vascular walls and extracellular interstitium: 1=mild; 2=mild to moderate; 3=moderate; 4=moderate to severe; 5=severe. Online supplementary table S2 provides detailed information about scoring amyloid deposits.

Table 3 Proportion (%) of WT TTR in amyloid-forming TTR

Tissue	LT1	LT2	LT3	LT4	Ave	p Values*	NL1	NL2	NL3	NL4	NL5	NL6	NL7	Ave
Peripheral nerve														
Sciatic nerve	97	70	76	97	85	<0.01	NE	NE	26	NE	25	36	NE	29
Median nerve	NE	97	NE	94	96	NA	NE	NE	43	NE	NE	NE	NE	NA
Sympathetic nerve	78	89	NE	95	87	NA	NE	NE	NE	NE	33	NE	NE	NA
Spinal cord	6	3	24	22	14	0.54	NE	23	8	NE	ND	26	NE	19
Kidney	89	ND	76	98	88	<0.01	25	NE	18	26	ND	20	18	21
Thyroid gland	91	51	62	96	75	<0.01	48	NE	23	NE	42	30	NE	36
GI tract														
Small intestine	NE	96	85	89	90	<0.01	NE	52	NE	57	36	50	NE	49
Large intestine	NE	99	NE	96	98	NA	NE	35	NE	NE	53	43	NE	44
Heart	91	91	86	94	91	<0.01	50	51	39	45	59	45	NE	48
Tongue	84	89	NE	95	89	NA	NE	NE	NE	NE	53	72	NE	63
Lung	98	94	81	94	92	<0.01	51	66	40	NE	53	34	NE	49

*p Values according to Student's t test.
Ave, average; GI, gastrointestinal; LT, patients who underwent LT; NA, not applicable; ND, peaks derived from TTR not detected; NE, not examined because of non-availability of frozen tissue specimens; NL, non-LT patients; TTR, transthyretin; WT, wild-type.

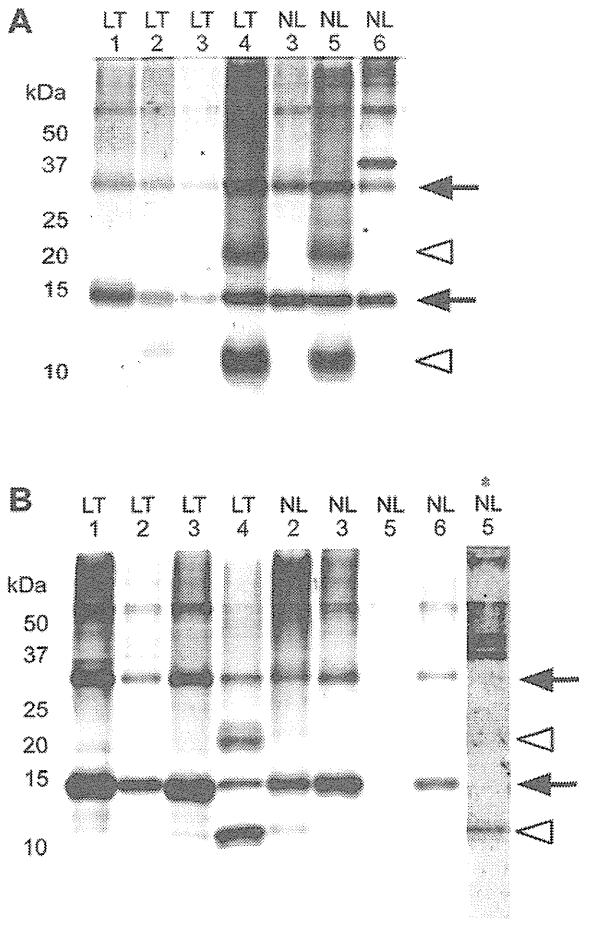

Figure 2 Immunoblotting for the detection of the truncated form of transthyretin (TTR). (A) TTR extracted from amyloid deposits in the sciatic nerve of patients with and without LT. (B) TTR extracted from amyloid deposits in the spinal cord of patients with and without LT. Arrows and arrowheads indicate bands derived from full-length TTR and truncated TTR, respectively. LT, patients with LT; NL, non-LT patients. *NL5: extended detection time.

To verify the hypothesis that certain pathological relationships exist between FAP long after LT and SSA, a sporadic systemic amyloidosis formed by WT TTR which is partially truncated,[13 14] we investigated three issues: 1) histopathological findings in systemic tissue sites, 2) proportion of WT TTR in amyloid deposits in systemic tissue sites and 3) truncation of TTR in amyloid deposits of FAP patients.

Histopathological features of FAP ATTR V30M patients long after LT were strikingly different from those of non-LT patients. SSA is an age-related systemic amyloidosis and affects mainly cardiac functions.[13 14] Our detailed systemic histopathological examinations revealed that tissue sites with relatively severe amyloid deposits in patients long after LT seemed to be similar to tissue sites with amyloid deposits in patients with SSA,[13 22–24] except for the spinal cord in which amyloid deposits are thought to be formed by the polymerisation of TTR secreted from the choroid plexus of the brain.

In the kidney of non-LT patients, only case NL5 originating from an FAP-non-endemic area showed slight amyloid

Table 4 Predominant forms of TTR in amyloid deposits

	Full-length TTR (20 cases)	Truncated and full-length TTR (9 cases)	p Value*
Liver transplantation			
Underwent	3 (15%)	1 (11%)	0.37
Not underwent	17 (85%)	8 (89%)	
Residence			
Endemic area (Kumamoto)	20 (100%)	1 (11%)	<0.0001
Non-endemic areas	0 (0%)	8 (89%)	
Age at examination			
Less than 50	10 (50%)	2 (22%)	<0.0001
Fifty and more	10 (50%)	7 (78%)	
Sex			
Male	10 (50%)	9 (100%)	<0.0001
Female	10 (50%)	0 (0%)	

*p Values according to Pearson's χ^2 test, comparing each group with the other groups.
TTR, transthyretin.

deposition, while moderate-to-severe amyloid deposits were found in the other non-LT patients originating from an endemic area, including NL6 and NL7 that were older than NL5. Koike *et al*[25] also reported that late-onset FAP ATTR V30M patients originating from an FAP-non-endemic area showed mild amyloid deposits in the kidney. Based on these findings, we speculate that FAP ATTR V30M patients originating from an endemic area may have some genetic or environmental factors enhancing renal TTR amyloid formation, other than the age of onset.

Mass spectrometric analyses revealed that amyloid deposits in systemic tissues, except for the spinal cord, in patients long after LT derived mostly from WT TTR, which was secreted from the normal liver graft. These results agree with several other studies examining the heart,[11 12] peripheral nerves[26] and abdominal fat[11 27] in patients undergoing LT. Those data together indicate that FAP ATTR V30M long after LT seems to be similar to the process occurring in SSA with regard to histopathological findings and proportion of WT TTR in amyloid deposits in systemic tissue sites.

Liepnieks and Benson reported that the proportion of WT TTR in cardiac amyloid deposits was greater in an FAP ATTR V30M patient who died 3.8 years after LT (80%) than in another patient who died 1.5 years after LT (65%).[12] Ihse *et al*[11] also reported that the proportion of WT TTR in cardiac amyloid deposits was 96% in an FAP ATTR V30M patient who died 7 years after LT. In the present study as well, cardiac amyloid deposits in patients 10 years after LT were derived mostly from WT TTR (86%–94%). One patient (case LT3 in table 1) who underwent LT at an advanced stage of disease, more than 7 years after FAP onset, had a lower proportion of WT TTR (86%) in cardiac amyloid deposits than did other patients (cases LT1, LT2 and LT4 in table 1) who underwent LT 0.6 to 2.5 years after the onset of FAP (table 3). These results suggest that old amyloid deposits derived from MT TTR before LT gradually dissociate or are subject to turnover, and WT TTR continues to form new amyloid deposits after LT.

On the other hand, non-LT patients had a relatively high proportion of WT TTR in several tissues such as the heart and tongue, but a relatively low proportion in others such as the nerves, kidney and thyroid gland (tables 2 and 3). A previous study also reported a high proportion of WT TTR in cardiac amyloid deposits in patients from non-endemic areas of Japan.[28] It is interesting that those tissue sites with relatively high proportions of WT TTR in amyloid deposits in non-LT patients evidenced relatively severe amyloid deposition in patients long after LT, but tissue sites with relatively low proportions of WT TTR in amyloid deposits in non-LT patients had mild amyloid deposition in patients long after LT, except for the spinal cord (tables 2 and 3). These findings suggest that several organs developing severe amyloid deposits after LT, such as the heart and tongue in which amyloid deposits derived mostly from WT TTR, may have specific tissue factors that are associated with developing WT TTR amyloid in FAP patients with LT and those without LT and that these tissue factors differ from those associated with MT TTR amyloid formation. One possibility is that aging of the tissue matrix caused by long-term mechanical stress enhances amyloid formation in those tissue sites.[23]

We also clarified the biochemical features of amyloid deposits in the central nervous system (CNS) of FAP ATTR V30M patients with and without LT. As table 3 shows, amyloid deposits in the spinal cord consisted mostly of MT TTR in patients with and without LT. These findings suggest that LT may not prevent progression of CNS amyloidosis, which reportedly causes fluctuating mental status and haemorrhage in some FAP patients,[29 30] because the CNS is a distinct tissue site in which amyloid deposits derive from MT TTR mainly synthesised by the choroid plexus even after LT.

Together, our histopathological and biochemical studies suggest that FAP ATTR V30M patients after LT develop WT TTR amyloid deposits in systemic organs except for the CNS. However, the reasons why WT TTR amyloid deposits, which are usually found in elderly SSA patients, occur in relatively young FAP patients after LT remain to be determined. One possibility is that older amyloid deposits formed by MT TTR before LT may act as a nidus, which enhances polymerisation of proteins,[31] and additional WT TTR amyloid fibrils may form after LT because of a nucleation-dependent polymerisation, although in vitro TTR amyloid formation reportedly did not depend on nucleation.[32] Another possibility is that older MT TTR amyloid deposits may induce overproduction of basement membrane components, which may promote increased amyloid formation, as our previous study of non-LT FAP patients showed.[33] We therefore believe that WT TTR amyloid formation after LT at least partially depends on MT TTR amyloid deposits that existed before LT.

Amyloid deposits in SSA patients contain, in addition to full-length WT TTR, truncated C-terminal WT TTR fragments starting at positions 46–52.[13 14 34] Several studies also indicated that certain late-onset Swedish FAP ATTR V30M patients also have the truncated TTR in amyloid deposits.[11 34 35] Similarly, we found the truncation of TTR in amyloid deposits was related to age in Japanese FAP patients. Recently, Gustafsson *et al*[36] reported differences between Swedish FAP patients with and without the truncated TTR in amyloid deposits, in heart structure and function and clinical outcome after LT. The specific functional and pathological roles of the truncated TTR remain to be determined, however. In this study, although the truncation of TTR in amyloid deposits did not depend on undergoing LT, we elucidated the truncation of TTR occurred predominantly in patients from non-endemic areas of Japan, where FAP ATTR V30M patients have different clinicopathological features, such as late onset and low penetrance, compared with patients from an endemic area of Japan.[4] Those findings suggest that some unknown genetic or environmental factors may be involved in the truncation of TTR, which might be related to their clinical phenotypes. Further investigations should be needed to clarify those issues.

A limitation to this study is that we only investigated limited number of specimens from FAP ATTR V30M patients. Those findings need to be confirmed in a bigger number of patients. It is also interesting to investigate those histopathological and biochemical findings in FAP patients with other amino acid substitutions of TTR.

In conclusions, FAP may shift to systemic WT TTR amyloid formation after LT, which seems to be similar to the process in SSA, but WT TTR amyloid deposits may also be associated with old MT TTR amyloid deposits that existed before LT. The truncation of TTR in amyloid deposits may depend on some genetic or environmental factors other than undergoing LT.

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Competing interests None.

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Changes in pathological and biochemical findings of systemic tissue sites in familial amyloid polyneuropathy more than 10 years after liver transplantation

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REVIEW Open Access

Recent advances in transthyretin amyloidosis therapy

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Abstract

Mutant (MT) forms of transthyretin (TTR) cause the most common type of autosomal-dominant hereditary systemic amyloidosis—familial amyloidotic polyneuropathy (FAP). Until 20 years ago, FAP was thought to be an endemic disease, but FAP is known to occur worldwide. To date, more than 130 mutations in the TTR gene have been reported. Genotype-phenotype correlations are seen in FAP, and some variation in clinical presentation is often observed in individual kindreds with the same mutation and even among family members. Of the pathogenic TTR mutations, Val30Met was the first to be identified and is the most frequent known mutation found throughout the world. Studies of patients with FAP amyloidogenic TTR (ATTR) Val30Met documented sensorimotor polyneuropathy, autonomic dysfunction, heart and kidney failure, gastrointestinal tract (GI) disorders, and other symptoms leading to death, usually within 10 years of the onset of disease. Diagnosis is sometimes delayed, especially in patients without a clear family history and typical clinical manifestations, since diagnosis requires various studies and techniques such as histopathology, genetic testing, and mass spectrometry. For treatment of FAP, liver transplantation (LT) reportedly halts the progression of clinical manifestations. Exchange of an FAP patient's diseased liver with a healthy liver causes MT TTR in the body to be replaced by wild-type (WT) TTR. Although clinical evaluations indicated that progression of other clinical symptoms such as peripheral neuropathy, GI symptoms, and renal involvement usually halted after LT in FAP ATTR Val30Met patients, recent studies suggested that LT failed to prevent progression of cardiac amyloidosis in FAP ATTR Val30Met patients after LT, with this failure reportedly being due to continued formation of amyloid that derived mainly from WT TTR secreted from the transplanted non-mutant liver graft. In recent years, many therapeutic strategies have been proposed, and several ongoing therapeutic trials involve, for example, stabilizers of TTR tetramers (tafamidis and diflunisal) and gene therapies to suppress TTR expression (antisense methods and use of small interfering RNAs). These novel therapies may prove to prevent progression of FAP.

Keywords: Transthyretin, Amyloidosis, Familial amyloidotic polyneuropathy, Senile systemic amyloidosis, Immunotherapy, Gene therapy

Introduction

Mutant (MT) forms of transthyretin (TTR) cause the most common type of autosomal-dominant hereditary systemic amyloidosis—familial amyloidotic polyneuropathy (FAP) [1-3]. In recent years, many therapeutic strategies have been proposed, and several therapeutic trials for FAP are ongoing [4,5]. Here, we review clinical presentation, pathogenesis, diagnostic purpose, and recent advances in the treatment of this disease.

Amyloidosis and TTR

Amyloidosis is a protein conformational disorder characterized by extracellular accumulation of amyloid fibrils derived from various proteins [6-8]. Thus far, 30 distinct protein precursors of amyloid fibrils have been identified as causing different kinds of amyloidosis [9-12]. Depending on the type of amyloidosis, various factors can be responsible for protein aggregation.

TTR, a major amyloidogenic protein, is mainly synthesized in the liver [13] but also in the choroid plexuses of the brain [14], retinal pigment epithelial (RPE) cells of the eye [15], and α-cells of pancreatic islets [16]. TTR forms a homotetramer that has a dimer-of-dimers configuration in the bloodstream and that acts as a plasma transport

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