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【 ORIGINAL ARTICLE 】

Practice of Hereditary ATTR Amyloidosis in Non-endemic Areas of Japan

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Abstract:

Objective Hereditary ATTR (ATTRv) amyloidosis was once an incurable disease; however, in recent years, disease-modifying therapies, such as tafamidis and patisiran, have become available. We herein report the medical care situation in an ATTRv amyloidosis non-endemic area of Japan.

Methods We confirmed the information in the medical records of our department and analyzed the data retrospectively.

Patients Patients with ATTRv amyloidosis who were treated in our department between 2010 and 2021 were included.

Results A total of 15 ATTRv amyloidosis cases (8 men and 7 women) were treated in our department during the study period; 9 patients had a family history, and the *transthyretin* V30M (p.V50M) gene mutation was present in 66% of cases. The average age of the onset was 57 years old, with 73% of the initial symptoms being dysesthesia and 13% being autonomic dysfunction. Ten patients were treated with tafamidis and nine with patisiran. Although it took a long time to start treatment among our experienced cases, there were some cases in which treatment could be introduced relatively early.

Conclusion ATTRv amyloidosis is treatable and should be included in the differential diagnosis of neuropathy so that it can be diagnosed early and introduced into treatment. In the near future, the presymptomatic diagnosis of ATTRv amyloidosis and genetic counseling will become more important.

Key words: amyloidosis, hereditary, transthyretin, tafamidis, patisiran

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Introduction

Hereditary ATTR (ATTRv) amyloidosis is an autosomal dominant systemic amyloidosis causing multiorgan dysfunction with amyloid deposition involving the peripheral nerves, autonomic nervous system, cardiac muscle, kidneys, and gastrointestinal tract (1). ATTRv amyloidosis often occurs in people in their 20s and 30s, and symptoms deteriorate progressively, with an average survival duration of approximately 10 years in the natural history of patients in endemic areas, such as Nagano and Kumamoto in Japan (2).

The most common abnormal *transthyretin (TTR)* mutation in ATTRv amyloidosis is V30M (p.V50M). In addition, various other *TTR* mutations, such as S50R (p.S70R), E61K (p.E81K), and Y114C (p.Y134C), have also been reported (3). In contrast, in non-endemic areas, the onset tends to be relatively old, the family history is unclear, and autonomic dysfunction is unnoticeable (4).

ATTRv amyloidosis was previously regarded as an incurable disease without radical therapy. Liver transplantation began in the 1990s, followed by tafamidis and patisiran in

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the 2010s. Tafamidis stabilizes the TTR tetramer and inhibits its amyloid formation (5). Patisiran uses RNA interference to degrade TTR mRNA and inhibits the expression of the TTR protein in the liver (6). In recent years, several disease-modifying therapies have arisen as alternatives to liver transplantation. With the advent of new therapies, the concurrent introduction of genetic testing has meant that the number of newly diagnosed ATTRv amyloidosis cases has increased in non-endemic areas, even when a family history was unclear. In addition, although Hokkaido, where our facility is located, is not an endemic area, many families have migrated from all over Japan since the 19th century, and it can be said to be a microcosm of Japan as a whole.

In this study, we analyzed the trends in ATTRv amyloidosis in Hokkaido by analyzing the information of patients diagnosed and treated in our department.

Materials and Methods

The participants were consecutive patients with ATTRv amyloidosis who had a history of consulting our department between January 2010 and December 2021. We summarized the basic information, family history, clinical symptoms, course, gene mutation, and treatment content, and retrospectively evaluated and examined the disease tendency. In cases where a scale evaluation was possible, symptoms were evaluated using the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) (7) before and after treatment.

This study was approved by the institutional review board of our hospital (020-0066). Written or opt-out consent was obtained from patients and their families.

Results

We enrolled 15 patients with ATTRv amyloidosis, and their backgrounds are summarized in Table. The patients included 8 men and 7 women, and the average age of the onset was 57.1±16.8 years old. The time required from the first visit to the diagnosis was 5.0±6.8 years. Orthopedics was the most common department visited by the patients for the first time before visiting our department. Lumbar canal stenosis and cervical canal stenosis were often the initial diagnoses. Nine patients (60%) had a family history of the disease. Cases 2 and 6 were families from the endemic area. V30M (p.V50M) was the most common mutation, being noted in 10 cases, followed by Y114H (p.Y134H) in 2 cases and A120S (p.A140S), S50R (p.S70R), and E92K (p.E112K) in 1 case each. Dysesthesia was the most common initial symptom. All symptoms, including the subsequent course, were as follows: 1) somatic neuropathy, 14/15 (93.3%), 2) cardiomyopathy, 11/15 (73.3%), and 3) autonomic dysfunction, 6/15 (40%). Regarding peripheral neuropathy, dysesthesia (14/15 cases, 93.3%) was more common than muscle weakness (10/15 cases, 66.7%). Gastrointestinal symptoms (6/15 cases, 40%) and orthostatic hypotension (5/15 cases, 33.3%) were relatively common in autonomic dysfunction. Regarding cardiovascular findings, left ventricular wall thickening (9/15 cases, 60%) was common, but conduction disturbance (3/15 cases, 20%) was less so. At the time of the diagnosis, the myocardium (8/15 cases, 53.3%) was the most common biopsy site where amyloids were detected.

Regarding treatment, there were 5 cases in which tafamidis was started and changed to patisiran. Tafamidis was used in 10 cases and patisiran in 9 cases, and more recently, tafamidis was used in 4 cases and patisiran in 7 cases. There were two cases in which no therapeutic drugs were used. The main reason for the drug change was not the side effects of tafamidis but the desire for more effective treatment. Of these 15 patients, 11 were undergoing outpatient treatment at our department. One patient died of cancer, and three were transferred to other hospitals. Patients who continued patisiran showed less ATTRv amyloidosis symptom progression than natural history. The Norfolk QOL-DN was assessed before and after treatment in five patients, and the scores remained almost unchanged during the first year of treatment. In case 6, a pre-symptomatic diagnosis was made through genetic counseling, and an annual abdominal fat tissue biopsy was performed. After confirming amyloid deposition, treatment was started. Disease-modifying therapies were able to be introduced in this case before the symptoms progressed.

Discussion

According to a survey conducted by the Ministry of Health, Labor and Welfare of Japan between 2003 and 2005, the prevalence of ATTRv amyloidosis was 0.87-1.1 per million people, with the prevalence being the highest in Nagano Prefecture, followed by Kumamoto Prefecture and Ishikawa Prefecture (8). The population of Hokkaido was 5.28 million in 2019. The present report included a larger number of patients with ATTRv amyloidosis than previous reports. In addition to the fact that our hospital is a base for implementing advanced medical care in Hokkaido, it seems that an increasing number of patients in recent years have been going undiagnosed.

Previous reports of ATTRv amyloidosis in Japan included many cases of the V30M (p.V50M) variant. It has been reported that, in endemic areas, the onset is relatively young, occurring in the 20s and 30s, and dissociated sensory loss and autonomic dysfunction were typical, including many cases of cardiac conduction disturbance (2). However, ATTRv amyloidosis in non-endemic areas tends to differ from that in endemic areas in terms of the following: (a) unclear family history, (b) relatively late onset, (c) less dissociated sensory loss, (d) pain, (e) early distal muscle weakness, (f) less early autonomic dysfunction, and (g) cardiac hypertrophy but few cardiac conduction disturbances (4). A similar tendency was observed in the present study.

Regarding treatment, many patients switched from tafamidis to patisiran since the approval of the latter in Japan. However, there were cases in which the time from the onset

Table. List of 15 Consecutive Cases of Hereditary ATTR Amyloidosis Treated in Our Department from January 2010 and December 2021.

Case	Sex	Familial history	Onset age	Onset symptoms	First visit department	Initial diagnosis	Period from first visit to diagnosis (years)	*TTR* variant
1	M	Father, brother	63	Difficulty of walking	Neurology	CCS	0	V30M
2	F	None	36	Vomiting, constipation	Cardiology	SSS	0	V30M
3	M	Brothers and sisters	47	Numbness of extremities	Orthopedics	CTS, TTS	20	Y114H
4	M	None	58	Numbness of feet	Orthopedics	CCS	7	A120S
5	F	Brothers and sisters	50	Numbness of hands	Orthopedics	CTS	20	Y114H
6	F	Mother	24	Numbness of feet	Genetic counseling	ATTRvA	0	V30M
7	M	None	71	Weakness of feet	Orthopedics	LCS	3	V30M
8	M	None	69	Numbness of feet	Orthopedics	LCS	10	V30M
9	F	Sister	75	Weakness, numbness of hands	Neurology	Myopathy	1	V30M
10	F	Sister	65	Numbness of feet	Orthopedics	CTS	6	V30M
11	M	None	74	Numbness of extremities	Neurology	CIDP	2	V30M
12	M	Mother	28	Erectile dysfunction, dysuria	Urology	Autonomic dysfunction	3	S50R
13	F	None	67	Numbness of extremities	Orthopedics	CCS, LCS	2	V30M
14	F	Father	55	Numbness, breathlessness	Cardiology	HC	1	E92K
15	M	Sisters	74	Numbness of hands	Cardiology	Af	0	V30M

Case	Autonomic symptoms			Nerve conduction study findings				Cardiovascular findings	Histology	Treatment †
	OH	GI signs	Dysuria	DL	CMAP	CV	SNAP			
1	+	+	+	+	+	+	+	LVST, CDD	Myocardium	None
2	+	+	-	+	+	+	+	Sinus arrest	Myocardium	T
3	-	-	-	-	-	-	-	Within normal range	Ganglion, GI	T (discontinued)
4	-	-	-	+	+	+	+	LVWT, valve thickening	Myocardium	T, P, T
5	-	-	-	-	-	-	-	Within normal range	Carpal tunnel	None
6	-	+	-	-	-	-	-	Within normal range	AFT	T, P
7	-	-	-	+	+	+	+	LVWT, AVB	Myocardium	T, P
8	-	-	-	+	+	+	+	LVWT, VST	Myocardium, GI	T, P
9	+	+	+	+	+	+	+	LVWT	Skin	T
10	-	-	-	-	+	-	+	LVWT, valve thickening, AST	Skin	T, P
11	-	-	-	+	+	+	+	LVWT, LAE, CDD	Myocardium, GI	T
12	+	+	+	-	+	+	+	Bundle block, AVB	GI	LT, T, P
13	+	+	-	-	+	-	+	LVWT, VST	Myocardium, GI	P
14	-	-	-	+	+	+	+	LVWT, VST	Myocardium	P
15	-	-	-	-	-	+	-	Within normal range	None	P

M: male, F: female, CCS: cervical canal stenosis, SSS: sick sinus syndrome, CTS: carpal tunnel syndrome, TTS: tarsal tunnel syndrome, ATTRvA: hereditary ATTR amyloidosis, LCS: lumbar canal stenosis, CIDP: chronic inflammatory demyelinating polyneuropathy, HC: hypertrophic cardiomyopathy, Af: atrial fibrillation, *TTR*: transthyretin gene, OH: orthostatic hypotension, DL: prolonged distal latency, CMAP: decreased compound motor action potential, CV: decreased conduction velocity, SNAP: decreased sensory nerve action potential, VST: ventricular septal thickening, CDD: cardiac dilatation disturbance, LVWT: left ventricular wall thickening, AVB: atrioventricular block, AST: atrial septal thickening, LAE: left atrial enlargement, GI: gastrointestinal tract, AFT: abdominal fat tissue, T: tafamidis, P: patisiran, LT: liver transplantation

†: Treatments are listed in the order in which they were performed in each case.

to the diagnosis was long, and intervention was delayed. The results of a prior open-label trial suggest that early intervention could slow the progression of ATTRv amyloidosis symptoms (9). Furthermore, the use of patisiran did not trigger any deterioration in the symptoms of ATTRv amyloidosis but did improve the condition mildly in some cases (10). When treating patients with peripheral neuropathy, ATTRv amyloidosis should be considered as a differential diagnosis, and it is desirable to make an early diagnosis and start treatment as early as possible. Some cases of ATTRv amyloidosis may be treated as chronic inflammatory demyelinating polyneuropathy (CIDP), so the condition should be distinguished from CIDP in particular (11). In the present cases, amyloids were relatively frequently detected by a myocardial biopsy due to the fact that the cardiology department was active in the treatment of amyloidosis. Echocardiography and ^{99m}Tc-pyrophosphate scintigraphy may detect findings suggestive of cardiac amyloidosis, even if cardiac symptoms are not subjectively apparent, leading to amyloid detection by a myocardial biopsy. To diagnose ATTRv amyloidosis at an early stage, it is important to suspect its existence. If suggestive symptoms (red flags) are detected, ATTRv amyloidosis should be suspected, and genetic testing should be performed to detect amyloid deposition (12). The presence or absence of amyloids should be confirmed by a biopsy at multiple sites, including the skin, gastrointestinal tract, and myocardium. In fact, in case 6, the treatment course began with genetic counseling due to a family history, but a pre-symptomatic diagnosis was made, and early treatment was able to be introduced. A pre-symptomatic diagnosis is expected to become increasingly important in future ATTRv amyloidosis medical care.

A limitation of this study was the relatively small number of retrospective cases. If more large-scale prospective studies can be conducted in the future, more useful information can be obtained. Another limitation was that the period after the start of patisiran was insufficient, meaning that the therapeutic effect could not be confirmed. Furthermore, the TTR protein levels in the blood or cerebrospinal fluid could not be measured. In the future, it will be useful to be able to easily measure transthyretin protein as an objective therapeutic biomarker.

Conclusion

ATTRv amyloidosis in a non-endemic area has many different characteristics from cases in endemic areas, and the same was true in Hokkaido. ATTRv amyloidosis is a treatable disease, and it is important to consider this disease in the differential diagnosis of peripheral neuropathy and to actively consider genetic testing in order to start the diagnosis and treatment at an early stage. Early treatment with disease-modifying therapies is expected to suppress ATTRv amyloidosis progression. In the near future, the presymptomatic diagnosis of ATTRv amyloidosis and genetic counseling will become more important.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained for all participants, and the study was approved by the institutional review board of Hokkaido University Hospital.

The authors state that they have no Conflict of Interest (COI).

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