A Case of Familial Amyloid Polyneuropathy due to Phe33Val TTR with Vitreous Involvement as the Initial Manifestation

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Abstract

We report a 61-year-old Japanese woman with transthyretin (TTR) Val33-related familial amyloid polyneuropathy (FAP). She presented with late-onset, vitreous involvement as the initial manifestation, slow development of polyneuropathy, cardiomyopathy, and severe autonomic failure without carpal tunnel syndrome. Liver transplantation was performed and her postoperative course was stable. Taken together with previous reports, vitreous opacities seem to be common to Val33 FAP. Vitreous amyloidosis is usually seen in combination with the involvement of other visceral organs. The findings in the present case emphasize that vitreous opacities could be the first manifestation of FAP.

Key words: familial amyloid polyneuropathy, transthyretin, vitreous involvement

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Introduction

Familial amyloid polyneuropathy (FAP) is a group of autosomal dominant disorders caused by a mutant transthyretin (TTR). It is characterized by peripheral neuropathy, autonomic dysfunction, and the involvement of vital organs. About 100 different disease-causing mutations of the TTR have been reported (1-4). Since both normal and variant TTR are synthesized by the liver, liver transplantation is now the only way to control disease progression. TTR Met30 FAP (FAP type I) is the most common type of familial polyneuropathy in Japan, and is characterized by early onset, a high penetrance rate, marked autonomic dysfunction, and steady disease progression (5-7). Other major types are characterized by various clinical syndromes; however, the heterogeneity of clinical symptoms is recognized even for some mutations of the TTR gene. We report a case of FAP-related Phe33Val with vitreous involvement as the initial manifestation which was treated by successful liver transplantation; this is the first case of this mutation in Japan.

Case Report

The proband was a 61-year-old woman who initially noticed bilateral impairment of visual acuity at age 57. Over a 2-year period her vision deteriorated to counting fingers bilaterally. Slit-lamp biomicroscopy revealed extensive sheet-like vitreous opacity, and amyloid deposits were found in her eyes. Bilateral sequential pars plana vitrectomies were undertaken at age 59. She began to experience numbness in her toes at age 60. She developed progressive difficulty on walking and had a dull pain in her stomach. She was admitted with progressive anorexia, loss of weight and vitality, muscular weakness and numbness of the lower limbs, and recurrent diarrhea and constipation. She had lost 15 kg of body weight in the previous 4 years. Her mother had died at age 38 of renal failure, suggesting that she was affected with the same disease. Three elder sisters, two daughters,
and a son were otherwise normal. On admission, her blood pressure was 123/66 mmHg, heart rate 65 bpm, height 152 cm, and weight 38 kg. On neurological examination, she was alert and oriented without any cognitive deficits. She had bilateral visual loss. Muscle atrophy and weakness were noted predominantly in the distal extremities. Deep tendon reflexes were absent in all limbs and no pathological reflexes were observed. She had thermal and pain anesthesia with glove-stocking distribution, and decreased vibration and position sensation in the lower limbs. She could not perform heel-toe walking. There were no obvious abnormalities of the cerebellar system. She had postural hypotension (blood pressure 80/58 mmHg standing, 118/78 mmHg sitting) and recurrent diarrhea and constipation. Routine blood examination was normal. Cerebrospinal fluid analysis revealed normocytosis with an increased protein concentration of 206 mg/dL. Two-dimensional echocardiogram showed restrictive cardiomyopathy with concentric thickening of bilateral ventricles. Motor nerve conduction velocities (MCV) and the amplitude of compound muscle action potential (CMAP) were decreased in the bilateral tibial and peroneal nerves. No sensory nerve action potential (SNAP) was elicited in the bilateral sural nerves. Autonomic nervous system assessment revealed decreased cardiac frequency variability (RR Interval Variation) at rest and after hyperventilation, and decreased iodine-123meta-iodobenzyl guanidine (123I-MIBG) uptake in myocardial scintigraphy (Fig. 1). Brain and spinal cord magnetic resonance imaging (MRI) were normal without leptomeningeal enhancement.

TTR gene analysis was performed after the patient gave informed consent. Genomic DNA was extracted from the patient’s blood. All coding regions (exons 1, 2, 3, and 4) of the TTR gene were amplified by a previously reported PCR method (8), and examined by a direct sequencing method. The results revealed a heterozygous transversion T to G at nucleotide 183 in exon 2 of the published cDNA, which is predicted to change a phenylalanine to a valine at residue 33 of the mature protein (Phe33Val). To halt the progression of FAP, the patient underwent orthotopic liver transplantation and her early postoperative course was stable. Clinical and laboratory follow-up did not show any progression in the patient six months after transplantation.

**Discussion**

We report the present patient as having FAP with a Val33 TTR mutation. The clinical picture was characterized by the high age at onset, vitreous involvement as the initial manifestation, slow development of polyneuropathy, and severe autonomic failure. To date, Val33 FAP has been reported in 5 patients [2 British (9, 12), 2 Chinese (10, 13), and 1 Macedonian (11)], and thus our proband patient is the first identified in Japan (Table 1).

More than 100 mutation types in FAP patients have been identified to date, and Val30Met is considered to be the most common type that causes the classical phenotype of FAP. It is characterized by early onset, a high penetrance rate, marked autonomic dysfunction, and steady disease progression (5-7). On the other hand, the clinical features of non-Met30 FAP have been described as late onset, less serious autonomic dysfunction, and sometimes accompanied by cardiomyopathy, carpal tunnel syndrome, and central nervous system (CNS) symptoms. The present patient showed late onset, vitreous involvement, cardiomyopathy and marked autonomic dysfunction, including diarrhea, constipation, and orthostatic hypotension without carpal tunnel syndrome and CNS symptoms. Vitreous opacities are seen in approximately 20% of TTR mutations (4, 14-17). The prevalence of vitreous opacities is much higher in patients with ATTR Tyr114Cys (100%) than in those with ATTR Val30Met (24%) and is 0% within 5 to 10 years, and 17% at 10 years and later (17). Vitreous amyloid deposits can be the first indication of disease (14, 15), as in the patient described here. Although a few patients have been reported as having vitreous involvement in this Val33 mutation, our patient is the first case of vitreous involvement as the initial manifestation of this mutation. TTR amyloid in the vitreous of the eye is probably the result of synthesis by the retinal...
pigment epithelium (4). The predilection for fibril formation in the vitreous of the eye is not clear. The mechanisms involved in amyloid deposition in the vitreous may be similar to peripheral nerve or cardiac pathology, but an intriguing variation is that amyloid fibrils in the vitreous are greatly enriched (approximately 90%-95%) in variant TTR compared to 60%-65% in nerve and cardiac tissue of heterozygotes (18); however, it is not at all clear why there is a significant variation within families or why some TTR mutations show a very high degree of penetrance with ocular involvement. The findings in the present case emphasize that vitreous opacity could be the first manifestation of FAP.

With regard to FAP therapy, liver transplantation has been widely employed as the only potential cure for TTR-related FAP patients, since TTR is mainly produced in the liver. In the present patient, there has been no further deterioration, in contrast to the progression before transplantation. Statistical analysis indicates that patients with the Val30Met mutation are most likely to benefit and have 80% survival at 5 years. Patients with other TTR mutations, however, do not fare as well and show a 5-year survival of only 55%-60%. Many patients, especially those with TTR mutations other than Val30Met, show disease progression after liver transplantation (4). Further studies on TTR gene mutations as well as on patients affected by FAP and vitreous amyloidosis will be needed to elucidate the pathogenesis of these conditions further.

### References


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### Table 1. Clinical Features of Patients with Phe33Val TTR-FAP

<table>
<thead>
<tr>
<th>Authors</th>
<th>Report year (reference number)</th>
<th>Gender</th>
<th>Initial complaints</th>
<th>Age at onset (years)</th>
<th>Ethnicity</th>
<th>Cardiac dysfunction</th>
<th>Abdominal pain</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Urine retention</th>
<th>Carpal tunnel syndrome</th>
<th>ECG</th>
<th>Autonomic dysfunction</th>
<th>Vitreous opacity</th>
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<th>Paresthesia of four limbs</th>
<th>Weakness of lower extremities</th>
<th>Visual loss</th>
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