Case Report

Familial Amyloidotic Polyneuropathy in Hokkaido: A Case Report

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A 54-year-old man began to feel numbness in his hands at the age of 42 (1975). His condition became progressively worse accompanied by muscle weakness of the lower limbs and glove and stocking paresthesia of the extremities. The patient was admitted to our hospital on March 23, 1987. Neurological examination revealed distal dominant muscle weakness, sensory disturbance and areflexia. Electrocardiogram and ultrasound-cardiogram strongly suggested cardiomyopathy. A biopsy of the rectal wall and the cardiac muscle revealed amyloid deposits. The patient, his elder brother and one of his daughters had abnormal serum transthyretin (TTR, a protein referred as prealbumin). Therefore, the diagnosis of familial amyloidotic polyneuropathy (FAP) was confirmed. The patient's brother and daughter mentioned above, however, had no abnormal findings on physical examination and they were thus considered to be asymptomatic carriers. There may be more cases of asymptomatic carriers, if examination of abnormal TTR is more frequently analyzed.

Key words: Familial amyloidotic polyneuropathy, Transthyretin, Asymptomatic carrier

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant inheritance and is characterized by the deposition of amyloid fibers in various organs. In 1952, Andrade first described a case in Portugal and termed it FAP (1). Subsequently, there have been cases of FAP in the various countries including Sweden, Israel, Finland, Switzerland and Germany. In Japan, cases of FAP have been reported in only a few prefectures, notably Kumamoto and Nagano. FAP had not been previously reported in Hokkaido until the present case. The patient, his elder brother and one of his daughters had an abnormal TTR level. His brother and his daughter, however had no symptoms, and are therefore suggested to be cases of asymptomatic carrier.

CASE REPORT

A 54-year-old man was admitted to our hospital on March 23, 1987, because of muscle weakness of the hands and a tingling sensation in the extremities. The patient was born in Asahikawa, Hokkaido, Japan and his parents had come from Ishikawa prefecture. His father’s death was due to old age and his mother died of liver cirrhosis. We could not find any detailed information about his parents. There were no similar disorders in members of his family and also his family history showed no hereditary muscle or neurological disorder. He was a heavy drinker and smoker.

At age 42 and 49, he complained of numbness in the fingers, but, this subsided spontaneously within a month. At 44 years of age, impotence appeared, and at 51, he experienced numbness in his feet. Over a period of 2 or 3 months, this condition gradually worsened. Furthermore, edema in his extremities appeared after standing for a long time. At 52 years of age, muscle weakness of the upper limbs appeared. One year later, he noted difficulty of discrete movement of the hands, and muscle

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weakness of the lower limbs developed. At 54, he suffered from constipation, and he visited our hospital for a complete medical examination.

**Physical examination**

The height was 168 cm and weight, 60 kg. Pulse rate was 89 per minute, but irregular. Blood pressure was 132/84 mmHg in the supine position and it was 111/69 mmHg while standing. His scalp and facial skin seemed normal and there was no sign of macroglossia. A grade 2 systolic ejection murmur was heard in the fourth interspace in the left margin of the sternum. Hepatosplenomegaly were not noted. No other abnormal symptoms were observed.

Neurological examination revealed nothing abnormal in the mental status and cranial nerves, but he showed muscle weakness and atrophy in distal muscles. The grasping power was 7 kg. There was severe symmetrical disturbance of touch and pain sensation in the distal parts of all extremities. In addition, vibratory sensation was remarkably lost. The Achilles reflex was absent and other deep tendon reflexes were decreased. The Babinski reflex was absent. He showed a slight gate disturbance.

**Laboratory data**

In the laboratory data, there were no abnormalities with the exception of triglyceride, GPT, LAP and r-GTP levels. M-component was not detected on an electrophoresis. The results of the bone marrow study were unremarkable.

The posterolateral chest X-ray film showed slight cardiomegaly, and the cardio-thoracic ratio was 48%. An electrocardiogram showed frequent atrial premature beats. The QRS axis was $-80^\circ$ and there was QS deflection in leads V$_1$ through V$_4$ (Fig. 1). An ultrasound-cardiogram revealed a thickening of the interventricular septum (IVS) and posterior wall, and also a granular sparkling appearance was seen in the IVS (Fig. 2). The planar image of the thallium-201 myocardial scintigram was normal (Fig. 3a). The planar image of the technetium-99m-pyrophosphate myocardial scintigram showed diffuse and intense biventricular uptake of radio-nuclide (Fig. 3b). Cerebro-spinal fluid by lumbar puncture revealed 150 mmH$_2$O initial pressure and the fluid was clear, with a cell count of 3/mm$^3$ (lymphocyte), protein 83 mg/ml, and sugar 64
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Fig. 2. Two-dimensional ultrasonic-cardiography: a parasternal long axis view shows hypertrophy and granular sparkling appearance of the interventricular septum.

Fig. 3a. Planar image of thallium-201 myocardial scintigram shows normal left ventricular image with no right ventricular visualization.

Fig. 3b. Planar image of technetium-99m-pyrophosphate myocardial scintigram shows diffuse biventricular uptake of radionuclide.

mg/dl. Motor nerve conduction velocity measured in the median nerve was 35 m/sec. Sensory conduction velocity was not measurable due to the lack of a response. A nerve biopsy was performed at the sural nerve; Kluever-Barrera stained tissue showed nerve loss, but no abnormal deposits. The biopsy of cardiac muscle and rectal wall showed amyloid deposits. Microscopic examination of the cardiac muscle tissue showed amyloid deposits surrounding the myocardial fiber (Fig. 4a). Also microscopic examination of the rectal wall revealed amyloid deposits in the lamina muscularis mucosae (Fig. 4b). The amyloid fibril was determined to be non-AA protein as it was stained with Congo red even after exposure to potassium permanganate and dilute

Fig. 4a. Congo red staining of the myocardium: diffuse amyloid fiber deposition surrounds the nearly normal myocardial fiber.

Fig. 4b. Congo red staining of the rectal wall: amyloid deposition in the lamina muscularis mucosae can be seen.
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Fig. 5. Family tree of the patient. His elder brother and his daughter had abnormal serum transthyretin. The arrow is proposita.

The serum level of the abnormal TTR by RIA (3) was determined to be 11.29 mg/dl. In the familial study to which we referred, the patient’s elder brother and one of his daughters had a high level of serum abnormal TTR (Fig. 5). However, they showed no signs of FAP and had no abnormal findings in their electrocardiogram or ultrasound-cardiograms. The planar image of technetium-99m-pyrophosphate myocardial scintigram of his daughter was normal.

**DISCUSSION**

In Japan, there are two large foci of FAP, Arao city in Kumamoto prefecture and Ogawa village in Nagano prefecture. A few cases have also been reported in other prefectures (Kochi, Ishikawa, Tottori, Hyogo). To the present, there had been no reported case of FAP in Hokkaido. The patient’s parents were born in Ishikawa prefecture, but we could not demonstrate that his parents were a relation to the cases with FAP in Ishikawa reported by Kito et al in detail (4).

Amyloid was confirmed by biopsy of the cardiac muscle and rectal wall, and was stained by anti-transthyretin antiserum. These clinical manifestations and electrocardiogram and neuropathologic findings were consistent with those of classical FAP. We diagnosed this case as FAP. Although the patient had no family history of FAP, two in his family had abnormal TTR, especially his elder brother, who at the age of 62, was asymptomatic far beyond the usual age of onset of FAP. Since FAP is inherited as an autosomal dominant trait, and definite family history is usually present, we concluded that he was an aged asymptomatic carrier of FAP.

This FAP case is noteworthy because his elder brother and daughter had no symptoms of FAP, although they showed a higher abnormal TTR level than the patient. Until recently, it was thought that FAP did not skip generations and did not have asymptomatic carriers (5). However, there are some reports of spontaneous cases (6–8) and asymptomatic carriers (9). From these findings it can be concluded that the patients who have abnormal serum TTR do not always have FAP. And there may be families with FAP which have not been discovered as there is no one with the symptoms. The patient’s father lived to be 81 and his mother, 68, but they had no symptoms of FAP. As also his elder brother has no symptoms, we suspect that the carrier in this family is probably asymptomatic. In the reports on asymptomatic carriers to the present, only females have been considered to be asymptomatic carriers (9), but we believe that there is a male asymptomatic carrier in this family. Recently, abnormal serum TTR level has been said not to be consistently related to the period of onset, duration of illness or the condition (9–11). In FAP, there may be unknown genetic factors in addition to gender.

The onset of FAP is usually in the second or third decade, but in patients with FAP in Japan and Portugal, the onset has been as late as the fifth or sixth decade (12), and the progression after onset has been rapid. The course of the illness is progressive and invariably leads to death. The late onset type of FAP usually begins after the fourth decade (13). The initial symptoms in this case appeared at 42 years of age, and gate disturbance appeared ten years later. So this seems to suggest that this case is the late onset type. It cannot be determined whether the asymptomatic carriers are independent of the late onset type or whether they die before the onset. The patient’s elder brother, an asymptomatic carrier, must be followed carefully to determine whether he shows any clinical signs of the disease or not, and his daughter in the period of onset will also have to be followed carefully.

Although this family has abnormal serum TTR
level similar to the cases previously reported in Japan, the proposita progressed very slowly and two carriers in this family are still asymptomatic. These phenomena are very important in the understanding of the mechanism of onset and the treatment of FAP. If FAP was classified into benign FAP (late onset type or asymptomatic carrier with slow progression after onset) and malignant FAP (typical onset type, complete penetrance and early progression after onset), the benign FAP, in a family such as this one, could be discovered much more readily by using biochemical studies to determine the abnormal TTR.

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