A Case of Familial Amyloid Polyneuropathy Homozygous for the Transthyretin Val30Met Gene With Motor-Dominant Sensorimotor Polyneuropathy and Unusual Sural Nerve Pathological Findings

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Objective: To report a case of familial amyloid polyneuropathy homozygous for the amyloidogenic transthyretin (ATTR) Val30Met gene with motor-dominant sensorimotor polyneuropathy and unusual sural nerve pathological findings.

Methods: Mass spectrometry analysis and polymerase chain reaction–restricting fragment length polymorphism were performed. A right sural nerve biopsy specimen was obtained for histological investigation.

Setting: Academic medical center.

Results: A 56-year-old Japanese man living in a local town (Nakajima, Japan) in Ishikawa Prefecture, a nonendemic area of type I familial amyloidotic polyneuropathy, had vitreous amyloidosis, motor-dominant sensorimotor polyneuropathy, erectile dysfunction, and urinary incontinence. He had neither orthostatic hypotension nor indolent diarrhea. Restriction enzyme analysis with EcoT22 I of amplified DNA and mass spectrometry analysis revealed homozygosity for ATTR Val30Met. Of 8 family members, 5 were evaluated and found to be heterozygous for ATTR Val30Met; a family history found no relative with the similar neurologic disorders. The sural nerve biopsy specimen showed focal edema and an amyloid deposit in the subperineural tissue, associated with moderate loss of myelinated and unmyelinated fibers.

Conclusions: In addition to the findings characteristic of homozygosity for ATTR Val30Met such as vitreous amyloidosis and relatively less autonomic involvements, this case had the unique findings of motor-dominant sensorimotor polyneuropathy and unusual sural nerve biopsy specimen results.

Arch Neurol. 2001;58:1914-1918

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not report orthostatic dizziness or diarrhea. On admission, a chest x-ray revealed no increase in plasma cells. The patient did not have any muscle atrophy or sensory disturbances. At that time, he noticed blurred vision. In 1991, a right vitrectomy was performed. Amyloid was recovered from the vitreous material. At that time, the patient did not have any muscle atrophy or sensory disturbances. He noticed erectile dysfunction and dysuria in 1998. He first noticed muscle atrophy of his upper and lower extremities in July 1999 and was referred to the hematology group at our hospital, where a biopsy specimen of his lip disclosed an amyloid deposit, although a biopsy specimen of his bone marrow revealed no increase in plasma cells. The patient did not report orthostatic dizziness or diarrhea. On admission, his blood pressure was 110/76 mm Hg in the sitting and standing positions, his pulse rate was 68/min and regular, his body weight was 41 kg, and his height was 161 cm. Neurologically, his mental status was alert and well oriented to time, place, and person. Cranial nerves were well preserved, except for the right eye, which showed a sluggish light reflex and lens opacity. Significant symmetrical muscle atrophy and weakness of the upper and lower extremities were noted with distal predominance and marked fasciculation. Deep tendon reflexes were hypoactive in the upper extremities and areflexic in the lower extremities. The plantar response was flexor bilaterally. Pain and vibratory sensations were slightly decreased below the ankles, but position sense was well preserved. Findings from examination of the cerebrospinal fluid showed no abnormalities. Motor conduction velocity was markedly decreased at the right ulnar nerve (22.4 m/s), the right peroneal nerve (15.5 m/s), the left peroneal nerve (20.8 m/s), the right posterior tibial nerve (34.7 m/s), and the left posterior tibial nerve (34.6 m/s). Motor conduction was not evoked at the right median nerve. No significant conduction block was noted. Conversely, sensory conduction velocity was well preserved at the left median nerve (48.8 m/s) and the left ulnar nerve (50.4 m/s). Sensory conduction was not evoked at the right median and ulnar nerves. The F-wave conduction velocity was decreased at the right ulnar nerve (32.4 m/s) and the left peroneal nerve (29.8 m/s), but it was preserved at the left posterior tibial nerve (41.3 m/s). F waves were not evoked at the median nerves bilaterally, the left ulnar nerve, the right peroneal nerve, and the right posterior tibial nerve. An echocardiogram showed no cardiomegaly and a computed tomographic scan of the abdomen revealed no organomegaly. The patient's muscle atrophy progressed and his body weight was 36.6 kg in October 2000.

**METHODS**

**MASS SPECTROMETRY**

To screen a mutant TTR in serum, a mass spectrometer (Bruker Reflex; Bruker Franzen Analytik GmbH, Bremen, Germany) was used. Fifty microliters of test serum was mixed with 20 µL of an anti-TTR polyclonal antibody (Dako, Glostrup, Denmark) and assayed as described previously. In the proband’s serum sample, peaks of 13912 dalton that corresponded to ATTR Val30Met were predominantly observed and no normal TTR peaks were detected (data not shown).

**DNA ANALYSIS**

For screening ATTR Val30Met, polymerase chain reaction–restraining fragment length polymorphism (PCR-RFLP) was performed: PCR-RFLP showed a normal band of 195 base pair (bp) in a normal subject (Figure 1A, lane 1), an extra band of 115 and 80 bp associated with ATTR Val30Met mutation in the proband (Figure 1A, lane 2), and both bands in a heterozygous patient with FAP ATTR Val30Met (Figure 1A, lane 3). These results suggest that the proband was a homozygote with FAP ATTR Val30Met. The PCR-RFLP analysis for 8 family members revealed 5 heterozygotic ATTR Val30Met gene carriers (Figure 1B-C).

**SURAL NERVE FINDINGS**

Congo red staining and polarized light analysis of excised sural nerve showed amyloid deposit in the perineural and endoneural tissues (data not shown). After the specimen was embedded in epoxy resin and stained with toluidine blue, it showed focal edema and amyloid deposits in the subperineural tissue (Figure 2A-B). There was a moderate loss of myelinated fibers (3773 fibers per square millimeter) and unmyelinated fibers (14800 fibers per square millimeter). Myelinated fibers with thin myelin sheaths, indicative of remyelinated fibers, were noted. Numbers of both large- and small-diameter myelinated fibers decreased (Figure 2C). The 2-peak pattern of myelinated fibers was well preserved. Electron microscopic findings showed amyloid fibrils intermixed with collagen fibers in the subperineural tissue (Figure 2D).

Our patient had been well until 1989, when he noticed blurred vision. In 1991, a right vitrectomy was performed. Amyloid was recovered from the vitreous material. At that time, the patient did not have any muscle atrophy or sensory disturbances. He noticed erectile dysfunction and dysuria in 1998. He first noticed muscle atrophy of his upper and lower extremities in July 1999 and was referred to the hematology group at our hospital, where a biopsy specimen of his lip disclosed an amyloid deposit, although a biopsy specimen of his bone marrow revealed no increase in plasma cells. The patient did not report orthostatic dizziness or diarrhea. On admission, his blood pressure was 110/76 mm Hg in the sitting and standing positions, his pulse rate was 68/min and regular, his body weight was 41 kg, and his height was 161 cm. Neurologically, his mental status was alert and well oriented to time, place, and person. Cranial nerves were well preserved, except for the right eye, which showed a sluggish light reflex and lens opacity. Significant symmetrical muscle atrophy and weakness of the upper and lower extremities were noted with distal predominance and marked fasciculation. Deep tendon reflexes were hypoactive in the upper extremities and areflexic in the lower extremities. The plantar response was flexor bilaterally. Pain and vibratory sensations were slightly decreased below the ankles, but position sense was well preserved. Findings from examination of the cerebrospinal fluid showed no abnormalities. Motor conduction velocity was markedly decreased at the right ulnar nerve (22.4 m/s), the right peroneal nerve (15.5 m/s), the left peroneal nerve (20.8 m/s), the right posterior tibial nerve (34.7 m/s), and the left posterior tibial nerve (34.6 m/s). Motor conduction was not evoked at the right median nerve. No significant conduction block was noted. Conversely, sensory conduction velocity was well preserved at the left median nerve (48.8 m/s) and the left ulnar nerve (50.4 m/s). Sensory conduction was not evoked at the right median and ulnar nerves. The F-wave conduction velocity was decreased at the right ulnar nerve (32.4 m/s) and the left peroneal nerve (29.8 m/s), but it was preserved at the left posterior tibial nerve (41.3 m/s). F waves were not evoked at the median nerves bilaterally, the left ulnar nerve, the right peroneal nerve, and the right posterior tibial nerve. An echocardiogram showed no cardiomegaly and a computed tomographic scan of the abdomen revealed no organomegaly. The patient’s muscle atrophy progressed and his body weight was 36.6 kg in October 2000.

**COMMENT**

We found a family in which the proband is homozygous for ATTR Val30Met and 5 of the 8 family members are heterozygous for ATTR Val30Met. The patient’s parents, now deceased, were second cousins living in Nakajima, Ishikawa Prefecture, which is a nonendemic area of FAP type 1 in Japan. No kinship was found in the families from endemic areas such as Ogawa Village and Arao City, where the large foci of FAP ATTR Val30Met exist. Previously, Yoshinaga et al described 3 patients with FAP homozygosity for ATTR Val30Met living in Kanazawa City, Ishikawa Prefecture, about 70 km south of Nakajima. We could not find any common ancestors between the family in that article and the family of our patient. Further study is needed to determine whether Nakajima might be another endemic area of FAP type 1 in Japan.

The patient showed his first clinical symptom, vitreous amyloidosis, when he was 45 years old. This age of onset is younger than the average previously reported in homozygous cases of ATTR Val30Met (mean age ± SD, 57.3 ± 5.4 years; age range, 51-68 years). The patient noticed erectile dysfunction and dysuria at the...
age of 54 years and had motor-dominant sensorimotor polyneuropathy at the age of 55 years.

In addition to the clinical symptoms characteristic of homozygosity for ATTR Val30Met such as vitreous amyloidosis and less autonomic involvements (without orthostatic hypotension and diarrhea), the patient showed motor-dominant sensorimotor polyneuropathy with distally predominant muscle atrophy and marked fasciculation. Pain and temperature sensations were mildly involved, but vibratory sensation was spared. Nerve conduction velocity studies showed a predominant motor involvement. Patients with FAP type I usually have symptoms of sensory and autonomic neuropathy in their early courses and motor neuropathy later. Motor-dominant polyneuropathy in early-stage FAP type I has apparently been reported in only 3 patients. A case of primary amyloidosis with early motor-dominant neuropathy that mimicked lower motor neuron disease has been reported. Muscle weakness is noted in the patients with amyloid myopathy, which is a well-recognized, but rare, manifestation of amyloidosis. However, it is the primary amyloidosis that most often has involvement of skeletal muscle.

The present case disclosed unusual sural nerve biopsy specimen findings: focal edema and amyloid deposits in the subperineural tissue, associated with moderate loss of myelinated and unmyelinated fibers. The morphometric analysis revealed a relatively preserved 2-peak pattern of myelinated fibers. The previous studies of sural nerve biopsy specimens from patients with FAP type I revealed the deposit of amyloid substances within nerve fasciculus, selective loss of small myelinated and unmyelinated fibers, and predominant axonal degeneration. We could not see pathological findings of subperineural edema in the sural nerves of patients with homozygous ATTR Val30Met, Yoshihara et al reported 1 case showing a marked loss of amyloid deposits in the sural nerves.

Figure 1. A, Polymerase chain reaction–restricting fragment length polymorphism (PCR-RFLP) showed a normal band of 195 base pairs (bp) in a normal subject (lane 1), an extra band of 115 and 80 bp associated with amyloidogenic transthyretin (ATTR) Val30Met gene mutation in the proband (lane 2), and both bands in a patient with heterozygote familial amyloid polyneuropathy ATTR Val30Met (lane 3). M indicates DNA size marker. B, Polymerase chain reaction–restricting fragment length polymorphism analysis for 8 family members revealed 5 heterozygotic ATTR Val30Met gene carriers. M indicates DNA size marker; lane 1, normal control; lanes 2-9, family members evaluated; and lane 10, a patient heterozygous for ATTR Val30Met from a different pedigree. C, Pedigree of family. The arrow indicates the proband; circle, females; squares, males; daggers, dead; 6, 3, 2, 9, 4, 5, 7, and 8, all represent persons who were tested and these numbers correspond to the lane numbers in Figure 1B.
myelinated and unmyelinated fibers, but they did not find edema or an amyloid deposit in the subperineural tissue.

Patients homozygous for the ATTR Val30Met gene do not appear to suffer from more severe illness.6-8 Even asymptomatic homozygous ATTR Val30Met gene carriers have been described.7,8 However, most of the neurologic symptoms of FAP are due to infiltrated deposits of amyloid fibrils in the tissues. Characterization of the various amyloidogenic TTR mutations has set the stage for an effort to clarify the mechanisms underlying fibril formation. Amyloid fibrillogenesis has been considered a multifactorial process.21 The factors influence fibril formation in FAP, consist of the intrinsic conformation of the TTR fibril protein, its concentration, the structural effects of TTR mutation, microenvironments of the lysosome, proteolytic processing, amyloid cofactors and tissue-specific determinants.21 Therefore, the clinical phenotypic heterogeneity of TTR mutations can be explained by these complicated multifactorial mechanisms.

Accepted for publication March 30, 2001.

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