

Short report

Familial amyloidotic polyneuropathy without familial occurrence: carrier detection by the radioimmunoassay of variant transthyretin

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SUMMARY A 47 year old woman with familial amyloidotic polyneuropathy (FAP) is reported, without familial occurrence of the disease. Her 81 year old mother and 53 year old sister were proved to be asymptomatic carriers for variant transthyretin (TTR) by means of the radioimmunoassay. It is suggested that unknown factor(s) may play a role in preventing or delaying the onset of the disease, producing variations in sex and family incidence. In order to establish the diagnosis of non-hereditary primary amyloidotic polyneuropathy, it must be confirmed that variant TTR is absent in the serum of relatives.

Familial amyloidotic polyneuropathy (FAP) of Japanese origin is an autosomal dominantly inherited disorder with a high penetrance and equal sex ratio.^{1,2} The first symptoms usually appear during the third or fourth decade of life; the disease is progressive and is fatal in about 10 to 20 years. Recent studies have demonstrated that amyloid fibril protein derived from Japanese,³ Portuguese⁴ and Swedish⁵ types of FAP is a variant transthyretin (TTR) with a single amino acid substitution of a methionine for a valine at position 30. The serum of FAP patients contains this variant TTR along with normal TTR. Nakazato *et al*⁶ have developed a radioimmunoassay based on a non-peptide (position 22 = 30) of the variant TTR, which has led to the regular diagnosis of FAP by demonstrating abnormal serum levels of variant TTR.⁷

We describe a woman with FAP who has no family history of the disease but whose mother and elder sister were shown to be carriers of FAP with the variant TTR by radioimmunoassay. To our knowledge there has been no report of a similar family with FAP.

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Case report

A 47 year old Japanese woman was admitted to Gunma University Hospital because of insensitiveness to pain in her legs. At the age of 42 years, she noticed that her feet were insensitive to heat and pain, and she often suffered burns and injuries to the legs. Several months later, she experienced a bout of severe nausea, vomiting and diarrhoea for a few days. Then she regularly suffered from these symptoms around the time of menstruation. The sensory disturbance in the lower extremities and monthly attacks became worse and she gradually lost weight. She was born in Osato village, which is very inaccessible from Arao city¹ or Ogawa village.² Her parents were not consanguineous. Her father died from acute myocardial infarction at the age of 73. Her 81 year old mother and 53 year old sister were healthy and normal on neurologic examination. Ancestors of her mother were also from Osato village. Similar disorders were absent in other members of this family (fig 1).

The patient was emaciated. There were several areas of residual scarring of burns on the legs. Her blood pressure was 124/70 mm Hg without orthostatic hypotension. The lung, heart and abdomen seemed normal. A little pitting oedema was noticed on the legs. The patient was alert, well-oriented and cooperative. Her pupils were isocoric and showed prompt reaction to light. Other cranial nerves were normal. Distal muscles in extremities were mildly atrophic but their strength was well preserved. Deep reflexes were symmetrically diminished at the biceps brachii, absent at the

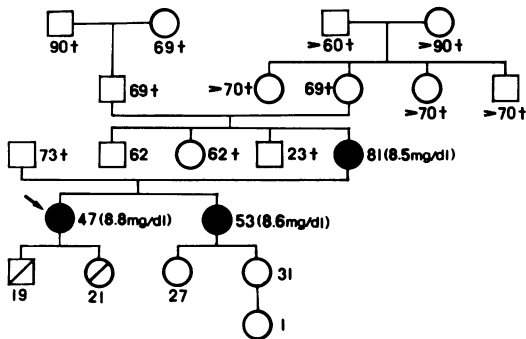


Fig 1 Pedigree of family. Symbols: \blacktriangle \bullet proband; \bullet asymptomatic carriers of variant TTR; \square \circ healthy person proved to be noncarrier of variant TTR. Others, \circ , \square are described as not having the disease. The ages of the individuals are indicated by the numbers or more than (>) numbers. Serum levels of variant TTR are shown in parentheses.

ankle and slightly hyperactive at the triceps brachii and the knee. Extensor plantar responses were not elicited. Disturbances of pain and temperature sensation were noted below the middle portion of the abdomen and increased in severity toward the feet to the extent of complete analgesia and thermanaesthesia. Tactile sensation was moderately disturbed below the knees and deep sensation was less impaired. The urinary and bladder disturbances were absent. Perspiration was markedly decreased in high temperature surroundings.

Laboratory studies were as follows: urinalysis showed increased sediments; stools were fatty; radiographs showed cervical canal stenosis; serum TTR, 16.6 mg/dl (normal, 30.5 ± 4.5 mg/dl); and variant TTR, 8.8 mg/dl (normal, undetectable). In the median nerve, motor and sensory conduction velocities were 48.3 m/s and 33.3 m/s respectively. Nerve potentials were not evoked in the peroneal and sural nerves. Normal studies included peripheral blood and bone marrow cell counts, routine blood biochemical and serological evaluations, immunoelectrophoresis, cell count and protein content of cerebrospinal fluid and electrocardiogram.

A specimen from the sural nerve disclosed amyloid deposits around vessels (fig 2). They were stained positively with Congo red and showed typical birefringence under polarisation microscopy. Both myelinated and unmyelinated fibres were markedly decreased in number. Amyloid deposits were also found in the gastric and rectal mucosae and the skin. Electronmicroscopic examination confirmed amyloid consisting of irregularly interlacing fibrils of 10 nm in diameter and an abundant formation of bands of B nger. The amyloid deposits were resistant to both treatments with the permanganate method and the autoclave method.⁸

Results of the radioimmunoassay determination of serum normal and abnormal TTR levels were 8.7 mg/dl and 8.5 mg/dl in her mother and 12.2 mg/dl and 8.6 mg/dl in her elder sister, respectively, indicating that the TTR gene was heterozygous and identical to that of the patient, who carried one normal and one mutant gene.⁹ The variant

TTR was negative in the patient's daughter and son. The abdominal adipose tissue obtained from her mother was shown to contain amyloid deposits. Nerve conduction velocities on her mother were all normal: median nerve motor, 52.1 m/s; median nerve sensory, 55.5 m/s; peroneal nerve motor, 42.8 m/s; and sural nerve sensory, 50.0 m/s.

Discussion

Amyloidotic polyneuropathy is common in patients with FAP and in some patients with primary amyloidosis. The clinical manifestations presented by our patient without familial occurrence could not be distinguished from those of non-hereditary primary amyloidotic polyneuropathy, if the radioimmunoassay of variant TTR were not performed. As FAP is an autosomal dominant disorder with a high penetrance rate, family members carrying an abnormal gene for FAP or variant TTR in their sera have been considered to develop FAP sooner or later.^{7 10} None of the family members of this patient, however, is known to have any kind of manifestations suggesting polyneuropathy. Furthermore, her 81 year old mother and a 53 year old sister were proved to have no neurological abnormalities on clinical evaluations, in spite of the elevated levels of variant TTR and the deposition of amyloid protein in the adipose tissue. It is evident that the existence of one mutant gene for variant TTR should imply abnormal levels of serum variant TTR but not always indicate a clinical development of FAP, as shown in this family. It seems probable that unknown factor(s) may prevent or delay the development of FAP in this family.

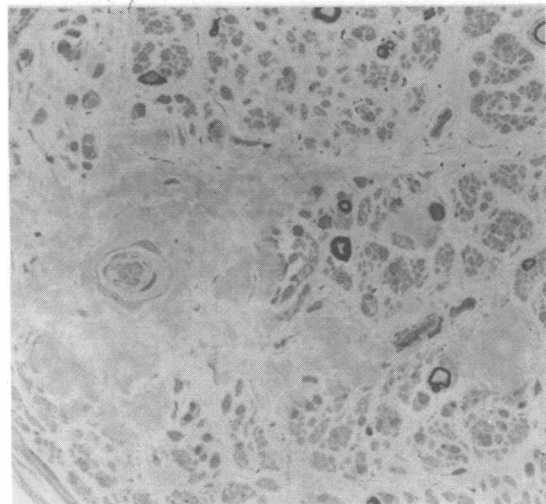


Fig 2 Biopsy specimen of sural nerve. Amyloid deposits are seen in perivascular area. Both myelinated and unmyelinated fibres are markedly decreased. (Toluidin Blue stain, original magnification, $\times 600$.)

Clinical investigations of FAP in Japan, Portugal and Sweden have shown that the age of onset and clinical manifestations of the disease may vary according to families, their localities and sex. In particular the sex difference seems most prominent. Female patients in Ogawa village (Japan) show later onset and slower progression than males.² The mean age at onset of Swedish cases is 45 years in men, about 10 years earlier than in women.¹¹ It does not seem only chance that the carriers in this family and a 65 year old carrier described by Saraiva *et al*⁴ are all females. The peculiarity of the family we have described is derived possibly from a familial tendency of late onset of the disease and female carriers outnumbering males. It is important to elucidate what makes the onset late or prevents it, for the mechanism may suggest how to treat the disease.

Finally, in a case suspected to be non-hereditary primary amyloidotic polyneuropathy the establishment of the diagnosis always requires evidence that serum abnormal TTR is absent, because it is difficult to distinguish from FAP only by signs and symptoms, when there is no familial occurrence. The family members and ancestors of our patient appear to have remained asymptomatic for life, in spite of possible possession of variant TTR in their sera. This fact indicates that it is important to weigh the natural history of this disease variable from patient to patient and family to family when genetic counselling is required.

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