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 al6 have developed a radioimmunoassay based on a nonapeptide (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.

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

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, ×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.\(^1,11\) 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.

References