Type I Familial Amyloidotic Polyneuropathy in Japan

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We studied 107 cases and 64 carriers of type I familial amyloidotic polyneuropathy (FAP) residing in 16 districts in Japan. The age of onset of illness ranged from 20 to 71 years old, with a mean of 40.1 ± 12.8 years (SD). One quarter of the cases were late-onset patients who developed the disorder after age 50. Asymptomatic carriers older than age 50 accounted for 20% of total carriers, with the oldest carrier being a 94-year-old woman. All the patients had a variant transthyretin with a methionine-for-valine substitution at position 30 with a mean serum level of 9.78 ± 3.27 (SD) mg/dl. The serum level did not significantly differ by gender in either patients or carriers, nor between patients and carriers. Incomplete penetrance of clinical expression was shown in eight cases. This study indicates that there is a considerable variety in age of onset, progression and geographic distribution of type I FAP in Japan.

Key words: FAP, variant transthyretin, radioimmunoassay

Introduction

Familial amyloidotic polyneuropathy (FAP) is an inherited systemic amyloidosis with autosomal dominant inheritance (1). Type I FAP, the subclass of FAP widely distributed throughout the world, usually starts between the twenties and forties with dissociated sensory disturbance in the lower extremities and autonomic dysfunction (1-3). As the disease progresses, sensory disturbance advances to affect the trunk and upper extremities as well, followed by motor neuropathy. Patients usually expire from cardiac or renal failure 10 to 15 years after onset (4). Two well-known conglomerations of families with type I FAP are found in Kumamoto and Nagano Prefectures of Japan (2, 3). Amyloid fibrils of type I FAP consist of a variant transthyretin, which has one amino acid substitution of methionine for valine at position 30 (5-7). This variant transthyretin, synthesized in the liver and choroid plexus, circulates in the serum and cerebrospinal fluid (8, 9). The amino acid substitution results from a base change from guanine to adenine at the first letter of the valine-30 codon of the transthyretin gene (10, 11). Type I FAP can be definitely diagnosed in a preclinical stage by identifying the variant transthyretin in the serum with radioimmunoassay (RIA) (12, 13) and the mutated transthyretin gene with Southern blotting technique (10, 11) or polymerase chain reaction (14, 15).

In the past 8 years, we have studied 107 cases of type I FAP and 64 asymptomatic carriers, who reside in 16 districts throughout Japan. We describe herein the geographic distribution of patients and carriers, their ages at onset, duration of illness, and serum levels of the variant transthyretin. Data were compared with those of classical type I FAP reported in the two well-known areas.

Subjects and Methods

Subjects

The subjects consisted of 107 cases (66 men and 41 women) of type I FAP, aged 26-76 years (45.2 ± 12.9; mean ± SD) and 64 healthy carriers (21 men and 43 women), aged 3-94 years (34.2 ± 19.5). Eight patients were admitted to our hospital and the other patients and carriers were investigated by the following hospitals located in Japan: Asahikawa Medical College (Hokkaido), Bibai Rosai Hospital (Hokkaido), Gunma University School of Medicine (Gunma), Hamamatsu Rosai Hospital (Shizuoka), Ishikawa Prefectural Central Hospital (Ishikawa), Hyogo Prefectural Amagasaki Hospital (Hyogo), Hiroshima University School of Medicine (Hiroshima), Kagawa Medical School (Kagawa), Kyoto City Hospital (Kyoto), Kyushu University School of Medicine (Fukuoka), Nagoya City University Medical School (Aichi), Nagoya National Hospital (Aichi), Nagoya University School of Medicine (Aichi), Ohmuta...
Rosai Hospital (Fukuoka), Oita Prefectural Hospital (Oita), Osaka University Medical School (Osaka), Tokyo Medical and Dental University School of Medicine (Tokyo), Tokyo Metropolitan Neurological Hospital (Tokyo), Faculty of Medicine, University of Tokyo (Tokyo), Tokyo Women's Medical College (Tokyo), Saga Medical School (Saga), Saiki Hospital (Iwate), Shinshu University School of Medicine (Nagano). All the subjects were heterozygotes for the mutated transthyretin gene. Geographic distribution of subjects is shown in Fig. 1. The diagnosis of type I FAP was made by typical clinical manifestations and confirmed by biopsy and serum Met\textsuperscript{30} transthyretin levels measured by RIA.

**Determination of serum Met\textsuperscript{30} transthyretin level**

The serum level of Met\textsuperscript{30} transthyretin was determined by an RIA as reported previously (12, 13). Briefly, 5 μl of the serum was treated with cyanogen bromide and trypsin, then subjected to RIA.

**Results**

Table 1 summarizes the ages of onset, duration of illness and serum levels of Met\textsuperscript{30} transthyretin in subjects. The distribution of age of onset of illness is shown in Fig. 2. The mean age of onset was 40.1 ± 12.8 years. The youngest age of onset was 20, the oldest was 71. No significant difference was noted in age of onset between male and female patients. Late-onset cases, who developed the disorder after age 50, accounted for 24% of total cases. Duration of illness ranged from one to 17 years, with no significant difference between male and female patients. All the patients had Met\textsuperscript{30} transthyretin in the serum ranging from 2.04 to 22.31 mg/dl with a mean of 9.78 ± 3.27 (SD). The serum levels were nearly equal between male and female patients.

The distribution of age of asymptomatic carriers is shown in Fig. 3. Out of carriers, 20% of subjects were older than age 50, and 2/3 of the aged carriers were women. Serum levels of Met\textsuperscript{30} transthyretin were not significantly different between male and female carriers, nor between patients and carriers.

**Discussion**

Clinical features, age of onset, and progression of Japanese type I FAP have been thought to be relatively constant based on studies of FAP-families with a homogeneous genetic background (2–4). Since the develop-

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![Fig. 1](image1.png)

Fig. 1. Geographic distribution of FAP patients and carriers studied. Numbers of patients and carriers are shown in that order.

![Fig. 2](image2.png)

Fig. 2. Histogram of age of onset of patients with type I FAP.

<p>| Table 1. Age of Onset, Duration of Illness and Serum Level of Met\textsuperscript{30} Transthyretin |
|-----------------|------------|-------------|-------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Age of onset (yrs)</th>
<th>Duration of illness (yrs)</th>
<th>Serum level of Met\textsuperscript{30} transthyretin (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>66</td>
<td>44±14</td>
<td>39±14</td>
<td>5±3</td>
</tr>
<tr>
<td>F</td>
<td>41</td>
<td>46±9.7</td>
<td>41±10.1</td>
<td>5±3.4</td>
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<tr>
<td>total</td>
<td>107</td>
<td>45±12.9</td>
<td>40±12.8</td>
<td>5.1±3.3</td>
</tr>
<tr>
<td>Carrier</td>
<td>21</td>
<td>27±17.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>43</td>
<td>34±20.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>total</td>
<td>64</td>
<td>32±19.8</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD.
Two cases and two carriers homozygous for the Met30 transthyretin gene were recently found in Japan (22, 23). The patients were 65 and 70 years old, and the carriers were 49 and 59 years old. All of them had double the usual serum level of the variant transthyretin in comparison to heterozygous cases, and all were relatively old. The presence of aged asymptomatic homozygotes for the mutated transthyretin gene indicates that the variant transthyretin is necessary for the development of FAP, but clearly is not a sufficient condition. Other genetic or environmental factors might be present that retard or prevent amyloid deposition in systemic organs, or factors required to produce fibrils might be absent even though the variant transthyretin is present in the serum at high levels as an amyloid precursor protein. Verification of the nature of such factors and their presence or absence is important in order to develop treatment and to provide appropriate genetic counseling.

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References


