Type I (Transthyretin Met30) Familial Amyloid Polyneuropathy in Japan

Early- vs Late-Onset Form

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Background: Type I (transthyretin Met30) familial amyloid polyneuropathy (FAP TTR Met30) occurs in 2 endemic foci in Japan. We have also reported late-onset Japanese cases unrelated to an endemic focus and showing distinctive clinicopathologic features.

Objective: To compare clinical and geographic features of FAP TTR Met30 between patients with onset before and after 50 years of age.

Design and Setting: Clinical information was obtained through a nationwide survey by the Study Group for Hereditary Neuropathy in Japan.

Results: Families with early-onset disease in this study numbered 82, and those with late onset, 59. In families with late onset, neuropathy showed male preponderance, low penetrance, little relationship to endemic foci, sensorimotor symptoms beginning distally in the lower extremities with disturbance of both superficial and deep sensation, and relatively mild autonomic symptoms. Families with early onset showed higher penetrance, concentration in endemic foci, predominant loss of superficial sensation, severe autonomic dysfunction, and atrioventricular nodal block requiring pacemaker implantation.

Conclusions: This study confirmed differences in clinical and geographic features between early- and late-onset FAP TTR Met30. Late-onset cases may be more prevalent and widespread than previously believed.

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Familial amyloid polyneuropathy type I (transthyretin Met30–associated familial amyloid polyneuropathy; FAP TTR Met30), in which methionine is substituted for valine at position 30 of transthyretin, is the most common type of familial amyloid polyneuropathy in Japan, as well as in Western countries. Typically, FAP TTR Met30 has been characterized by onset in the second or third decade of life, a high penetrance rate, marked autonomic dysfunction, loss of superficial sensation including nociception and thermal sensation, and steady progression of disease over 10 to 15 years. In Japan, these patients are concentrated in 2 geographic areas: the village of Ogawa in Nagano prefecture on the island of Honshu and the city of Arao in Kumamoto prefecture on the island of Kyushu. These patients with late-onset disease often are misdiagnosed initially as having chronic inflammatory demyelinating polyneuropathy or neuropathy of undetermined cause if DNA testing is not carried out. Thus, late-onset FAP TTR Met30 appeared to be geographically scattered throughout Japan, being difficult to diagnose without genetic analyses to detect the Met30 transthyretin mutation.

In the present study, we present results of a nationwide survey of FAP TTR Met30 performed by the Study Group for Hereditary Neuropathy in Japan. We assessed clinical and geographic features of early- and late-onset types of this disease. We confirmed the presence of a late-onset form of FAP TTR Met30, which occurred in families with no endemic focus and showed distinctive clinicopathologic features.
Table 1. Background and Clinical Features of FAP TTR Met30*

<table>
<thead>
<tr>
<th>Features</th>
<th>Early-Onset Group (n = 82)</th>
<th>Late-Onset Group (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean ± SD, y</td>
<td>31.9 ± 7.6</td>
<td>62.5 ± 6.2</td>
</tr>
<tr>
<td>Sex, No. M/F (ratio)</td>
<td>50/32 (1.56:1)</td>
<td>48/11 (4.36:1)</td>
</tr>
<tr>
<td>Presence of family history</td>
<td>77 (94)</td>
<td>28 (48)</td>
</tr>
<tr>
<td>Relationship to endemic foci</td>
<td>75 (91)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Initial complaint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic symptoms</td>
<td>47 (57)</td>
<td>48 (81)</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>39 (48)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Ocular symptoms</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Body weight loss</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial sensation–dominant</td>
<td>62 (76)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>All modality</td>
<td>20 (24)</td>
<td>41 (69)</td>
</tr>
<tr>
<td>Deep sensation–dominant</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are expressed as number (percentage) of patients, unless otherwise indicated. FAP indicates familial amyloid polyneuropathy; TTR, transthyretin.

METHODS

A nationwide survey was conducted by the Study Group for Hereditary Neuropathy in Japan, Nagoya, under the auspices of the Ministry of Health, Labor, and Welfare of Japan, Tokyo. The data of this study were based on 2 questionnaires. The first questionnaire was sent to 3098 hospitals with either more than 200 beds or more than 100 beds and a department of neurology. Physicians were asked whether any of their patients seen during the past 5 years had had FAP with a definite DNA diagnosis or suspected FAP based on diagnostic criteria of annual report of the amyloidosis research committee supported by the Ministry of Health, Labor, and Welfare of Japan. Patients with somatosensory neuropathy of undetermined cause with or without a family history also were investigated by DNA analysis. A response to the questionnaire was received from 1305 hospitals. A second questionnaire concerning detailed clinicopathologic and genetic information was sent to these hospitals. Finally, patients from 164 families with FAP were registered, with restriction to 1 individual per family. Of these families, 141 had the Met30 transthyretin mutation.

On the basis of previous reports, the 141 patients were divided into early- and late-onset groups in terms of symptom onset before or after 50 years of age.10,15,16 The group with early onset included 82 probands and the late-onset group included 59 probands. The mean age at onset in the early-onset group was 31.9 years, and in the late-onset group, 62.5 years. Presence of relationships to the 2 endemic foci of Japan was investigated in family members including at least the 2 most recent previous generations. The presence of neuropathy was defined clinically by symmetric impairment of muscle strength and sensation, accompanied by hyporeflexia or areflexia in the extremities. Nerve conduction studies and/or sural nerve biopsies were performed for confirmation.

All patients underwent a clinical examination by a neurologist. The second questionnaire was answered by these neurologists and concerned general physical and neurological findings including muscle strength, sensory disturbances, deep tendon reflexes, autonomic symptoms, results of nerve conduction studies, and, when available, sural nerve histopathologic findings. Autonomic involvement was characterized in terms of orthostatic hypotension, syncope, diarrhea or constipation, urination, sweating, and impotence. Orthostatic hypotension was defined as a fall of 30 mm Hg in systolic blood pressure on arising from the supine position. Recurrent episodes of diarrhea and constipation, urination, and incontinence, apparent hypohidrosis or episodes of excessive sweating, and complaints of impotence were defined as indicative of these autonomic symptoms. Severity of the autonomic symptoms of the late-onset cases in the endemic foci was assessed directly from the patients by the members of the research group.

To confirm the diagnosis of FAP TTR Met30, DNA analyses for mutation of the transthyretin gene were performed in all patients without a previous DNA diagnosis. Genomic DNA was extracted from leukocytes, and exon 2 of the transthyretin gene was amplified by polymerase chain reaction as described previously.10,17,18 After the polymerase chain reaction product was digested with the restriction enzyme NsiI, we determined whether digestion at the new site was evident on agarose gels stained with ethidium bromide. The DNA analyses were performed in the Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; the Third Department of Medicine, Shinsyu University School of Medicine, Matsumoto, Japan; the Third Department of Internal Medicine, Miyazaki Medical College, Miyazaki, Japan; or the Department of Laboratory Medicine, Kumamoto University School of Medicine, Kumamoto, Japan.

The Research Ethics Committee at each institution approved the study. The administrative facility for the investigation was at the Department of Neurology, Nagoya University Graduate School of Medicine. Informed consent was obtained by the physicians in the regional institutions and hospitals, and the study as a whole was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

RESULTS

GENETIC AND GEOGRAPHIC FEATURES

The early-onset group consisted of 50 men and 32 women (male-female ratio, 1.56:1) and the late-onset group included 48 men and 11 women (ratio, 4.36:1) (Table 1). A family history could be elicited for 77 (94%) of early-onset and 28 (48%) of late-onset cases. Residence of patients or family members in 1 of the 2 Japanese endemic foci for FAP TTR Met30 was noted in 75 (91%) and 6 (10%) of patients with early-onset disease and 48 (81%) and 10 (10%) of the early- and late-onset cases, respectively. Overall geographic distribution of early- and late-onset groups of patients differed markedly (Figure). Early-onset cases were largely restricted to the 2 major foci, while late-onset cases were distributed widely throughout Japan.

CLINICAL FEATURES

Initial symptoms were those of somatic neuropathy in 47 (57%) of patients with early-onset disease and 48 (81%) of patients with late-onset disease (Table 1). On the other hand, autonomic dysfunction was the initial complaint in 39 (48%) and 6 (10%) of patients in the early- and late-onset groups, respectively. No patient in the early-onset group manifested heart failure as an initial symptom, in contrast to 3 (5%) of those in the late-onset group. Decreased visual acuity caused by increased opacity of the
vitrous fluid occurred in no patient in the early-onset group but in 1 patient (2%) in the late-onset group. Weight loss was an initial complaint in 4 (5%) and 0 of these respective patient groups.

As for neuropathic symptoms, both groups manifested symmetric polyneuropathy with more marked involvement of the lower than upper limbs. All patients in the early-onset group manifested a sensory-dominant pattern with paresthesias in the distal parts of the extremities as an initial complaint, although weakness and atrophy of the limbs also appeared in the later phase of the disease. On the other hand, patients in the late-onset group showed distally accentuated weakness with muscle atrophy as well as sensory disturbance beginning in the early phase of disease. Sensory disturbance also was noted in the distal portion of the limbs. Pain and thermal sensation were impaired more than vibration and joint position sensation (ie, sensory dissociation) in 62 (76%) of the early-onset group and 18 (31%) of the late-onset group, while loss of all modalities was seen in 20 (24%) and 41 (69%) of the respective groups. Painful paresthesias were present more frequently in patients with early-onset disease.

With respect to autonomic dysfunction, patients in the early-onset group showed severe symptoms, beginning in the early phase of the disease. In contrast, most patients in the late-onset group did not note autonomic symptoms in the initial phase, although these appeared in the later phase. While almost all patients manifested some autonomic symptoms at some time point, these symptoms were more severe in the early- than in the late-onset group. Orthostatic hypotension was present in 57 (70%) of the early-onset group and 31 (53%) of the late-onset group. Decreased sweating, particularly in the distal part of the lower limbs, was observed in 41 (50%) and 30 (51%) of the early- and late-onset groups. Diarrhea and constipation were noted in 52 (63%) and 32 (54%) of the respective groups. Disturbance of urination was noted in 53 (65%) of the early-onset group and 23 (39%) of the late-onset group. Sexual impotence was present in 27 (54%) of 50 and 23 (48%) of 48 patients examined. Thirty-three (40%) and 7 (12%) of the early- and late-onset groups, respectively, had severe cardiac conduction block requiring pacemaker implantation. Orthostatic hypotension and gastrointestinal tract symptoms were the most prominent autonomic features in patients in the early-onset group interfering significantly with daily living. Weakness of the extremities rather than the autonomic symptoms was the main problem affecting daily living in the late-onset group.

In the late-onset group, patients with a link to endemic foci required special consideration. These patients included 1 man and 5 women, with a mean age of 61 years (Table 2). Four of the 6 patients had a family history of FAP TTR Met30. The initial symptom was paresthesias in the distal portion of the legs in 2 patients, recurrent episodes of diarrhea and constipation in 2, arrhythmia in 1, and decrease in visual acuity in 1. Sensory dissociation was seen in 4 of 6 patients, while loss of all
modalities was seen in 2. Autonomic symptoms were relatively severe and caused significant disturbance of activities in 4 patients. A cardiac pacemaker was implanted because of severe atrioventricular conduction block in 3 patients. These features were similar to those of the early-onset group as opposed to those of late-onset cases unrelated to endemic foci.

There were 8 families with early-onset disease in the nonendemic areas. Their clinical features and penetrance rate were similar to those in the endemic foci. Five of these families were clustered in the northern part of Kyushu island, not far from Arao city, but no apparent relationship was found.

COMMENT

In this study we presented distinctive clinical features and geographic distribution patterns in patients with early- and late-onset FAP TTR Met30 as identified by a nationwide multicenter survey. This result confirmed earlier impressions that late-onset FAP TTR Met30, defined by clinical onset after 50 years of age, shows a tendency toward male preponderance, a relatively low penetrance rate, geographic scattering with rare relationships to endemic foci, sensorimotor symptoms beginning in the distal lower extremities, initial involvement of both superficial and deep sensation, and relatively mild initial autonomic symptoms.15,19 Early-onset FAP TTR Met30, on the other hand, showed a higher rate of penetrance, concentration in endemic foci, predominant loss of superficial sensation, severe autonomic dysfunction interfering with daily living, and occurrence of atrioventricular nodal block leading to pacemaker implantation. This early-onset group was considered identical to the previously described common form of FAP TTR Met30 with a relationship to endemic foci. Before the availability of molecular diagnosis, patients with late-onset FAP TTR Met30 residing outside of endemic foci frequently were misdiagnosed as having polyneuropathy of undetermined cause or chronic inflammatory demyelinating polyneuropathy.20

The cause of these contrasting clinical and geographic features of cases with the same Met30 transthyretin mutation is not yet determined. The difference in the age at onset might in itself modify the clinical features, but previous studies21-23 suggested that expression level of plasma transthyretin does not influence the age at onset and severity of the disease. Discordant phenotypes of FAP TTR Met30 in monozygotic twins suggest that acquired factors can cause a difference in phenotypes.24 In studies of transgenic mice carrying the human mutant transthyretin gene, amyloid deposition showed a variable time course despite a consistently high plasma concentration of mutant transthyretin.25,26 This observation suggests that acquired factors unrelated to the mutant gene are involved in the distribution and timing of amyloid deposition. A feminized hormonal environment also might influence phenotype, particularly in late-onset FAP TTR Met30, which shows a male preponderance. Another possible explanation for phenotypic differences is differing genetic background factors that modify the expression or deposition of the mutant transthyretin. Studies of patients with FAP TTR Met30 in an endemic area of Portugal showed an age at onset and phenotype similar to early-onset FAP TTR Met30 cases in Japan.15,19,27 Portuguese patients without a family history showed a tendency toward later onset and a somewhat atypical geographic distribution, parallel our findings.27 Late-onset FAP TTR Met30 with atypical features including a low penetrance rate also was reported in English patients residing in the United States.28 The FAP TTR Met30 in Swedish endemic foci has been reported to show a relatively late age at onset, a tendency to manifest sensory neuropathy as an initial symptom rather than autonomic manifestations, and a low rate of penetrance, all differing from typical Japanese patients in endemic foci, possibly suggesting the influence of ethnic population-based genetic background. In our study, phenotypes among patients with late-onset disease linked to endemic foci were similar to the early-onset phenotype; most patients were female and had a family history of FAP TTR Met30, presence of sensory dissociation, severe autonomic symptoms, and, frequently to often, a need for pacemaker implantation. Taken together, these various findings support the presence of genetic factors modifying the phenotype. Early-onset cases in the nonendemic areas manifested similar phenotype to those in the endemic foci, rather than to sporadic late-onset cases. These cases did not have an apparent relationship to endemic foci, but some of their remote ancestors might have had such a relationship. Five families clustered in the northern part of Kyushu may create another endemic focus, but we suspect that they also relate to endemic foci in some of
their remote ancestors because of their proximity to Aroa city.

Another characteristic difference is that anticipation of age at onset is apparent in patients with the early-onset type, but is not obvious in those with the late-onset type. Similar anticipation also was reported in South American patients,28,29 who have a widespread genetic basis for the disease. Further study should be conducted with respect to environmental factors and haplotype analysis.

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REFERENCES


