Noninvasive cardiovascular findings in familial amyloid polyneuropathy

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SUMMARY  The cardiovascular system was examined in 19 cases of familial amyloid polyneuropathy. In a group of patients with neurological involvement, various cardiac abnormalities were common, including orthostatic hypotension, prominent apex cardiographic A waves, abnormal apical systolic waves (bulges), systolic murmurs, mid-systolic clicks, Q5 waves, atrioventricular block, left bundle-branch block, and abnormalities of ejection time and pre-ejection period. Though there was one case with pronounced cardiac abnormality despite a normal neurological state, and though cardiovascular symptoms appeared later than neurological symptoms, the degree of cardiac involvement generally paralleled the severity of the neurological disorder.

Familial amyloid polyneuropathy initially involves the peripheral and autonomic nervous systems and later affects the cardiovascular system. Little is known about the cardiovascular functional effects of the disease, apart from the electrocardiographic abnormalities, and there has been no precise comparison between cardiac and neurological findings in this disease. Therefore, we studied several families with this disorder in Aroa City, Kumamoto, where there is a very large incidence of this illness, in order to elucidate the type and severity of associated cardiac dysfunction using noninvasive methods.

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Table 1  Peripheral nerve function tests in 12 patients with abnormal neurological findings (the affected group)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Age at onset (y)</th>
<th>Duration (y)</th>
<th>Ulnar MCV (&lt;4.0 ms, 49 m/s)*</th>
<th>Median SCV (&lt;3.2 ms, 62 m/s)*</th>
<th>Peroneal MCV (&lt;7.0 ms, 43 m/s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 147</td>
<td>M</td>
<td>30</td>
<td>17</td>
<td>(5.4, 23.6)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2 447</td>
<td>F</td>
<td>40</td>
<td>9</td>
<td>(7.4, 64.5)</td>
<td>(2.6, 55.6)</td>
<td>NR</td>
</tr>
<tr>
<td>3 411</td>
<td>F</td>
<td>33</td>
<td>8</td>
<td>(4.7, 44.7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>4 371</td>
<td>M</td>
<td>31</td>
<td>6</td>
<td>(4.7, 49.0)</td>
<td>(2.8, NR)</td>
<td>NR</td>
</tr>
<tr>
<td>5 25</td>
<td>M</td>
<td>19</td>
<td>6</td>
<td>(4.3, 63.2)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>6 34</td>
<td>F</td>
<td>29</td>
<td>5</td>
<td>(2.5, 50.0)</td>
<td>(2.8, 59.7)</td>
<td>(6.9, 43.1)</td>
</tr>
<tr>
<td>7 34</td>
<td>M</td>
<td>30</td>
<td>4</td>
<td>(6.0, 40.2)</td>
<td>(4.5, 47.9)</td>
<td>NR</td>
</tr>
<tr>
<td>8 29</td>
<td>M</td>
<td>25</td>
<td>4</td>
<td>(3.3, 61.8)</td>
<td>(2.8, 67.7)</td>
<td>(4.0, 44.6)</td>
</tr>
<tr>
<td>9 29</td>
<td>M</td>
<td>27</td>
<td>2</td>
<td>(3.3, 58.5)</td>
<td>(0.6, 38.1)</td>
<td>(5.1, 40.5)</td>
</tr>
<tr>
<td>10 27</td>
<td>M</td>
<td>26</td>
<td>1</td>
<td>(2.4, 47.1)</td>
<td>(2.5, 61.4)</td>
<td>(5.9, 42.9)</td>
</tr>
<tr>
<td>11 31</td>
<td>F</td>
<td>31</td>
<td>2/12</td>
<td>(2.6, 63.4)</td>
<td>(2.3, 64.7)</td>
<td>(7.1, 52.6)</td>
</tr>
<tr>
<td>12 31</td>
<td>M</td>
<td>31</td>
<td>1/12</td>
<td>(3.6, 63.8)</td>
<td>(2.9, 61.1)</td>
<td>(6.0, 49.1)</td>
</tr>
</tbody>
</table>

Mean 34.5 ± 9.7

M, motor conduction velocity; SCV, sensory conduction velocity; * normal values (latency, minimum velocity); NR, no response to the nerve stimulations.

Subjects

We studied 12 cases, 7 men and 5 women, of familial amyloid polyneuropathy with neurological symptoms (the affected group), and 7 cases, 2 men and 5 women, without neurological symptoms (the non-affected group) (Table 1).

The average age of the affected group was 34-36 years. The duration of the disease ranged from 1-6 months to 17 years. On the basis of results of peripheral nerve function tests (measurements of motor and sensory nerve conduction velocities of ulnar, median, and peroneal nerves using Medelec MS6-1 Electromyograph) there were 7 cases showing no response to electric stimuli or a significant delay in
nerve conduction velocity. These cases were
designated the severe group.
The average age of the non-affected group was
33.9 years.

Method

Each subject underwent the following: (1) careful
historical review of symptoms related to the cardio-
vascular system, (2) physical examination of the
cardiovascular system, (3) standard 12-lead electro-
cardiogram, (4) polygraphic recordings of our
standard method (Sawayama et al., 1973), using
simultaneous phonocardiogram, apex cardiogram,
carotid arterial pulse, and jugular venous pulse. In
addition, measurements were made of the left
ventricular systolic time intervals (LVSTI) [total systolic
phase (Q-II), ejection time (ET), pre-
ejection period (PEP) and ET/PEP ratio] (Saw-
yama et al., 1973). The blood pressure was measured in
the supine position and after 3 minutes in the
sitting position.

Results

Tables 2 and 3 list the results of all observations,
and provide indications of statistical significance.
In the affected group the duration of subjective
cardiovascular symptoms was 0 to 4 years, which
was significantly shorter than that of the neuro-
logical symptoms. The main cardiovascular ab-
normalities were arrhythmias, syncopal attacks, and
orthostatic hypotension. The apex cardiogram
disclosed abnormal systolic waves (bulges) and
prominent A wave, while the phonocardiogram
showed significant systolic murmurs, mid-systolic
clicks, and gallop rhythms. Such abnormalities were
epecially obvious in the neurologically severe
group.

In contrast, in the non-affected group, arrhyth-
mias, prominent A wave, and systolic murmurs
were noted only in the patients with diabetes
mellitus and hypertension.

Fig. 1 shows one patient from the affected group
with an abnormal systolic bulge and mid-systolic
click.

The electrocardiograms of the affected group
showed infarction-like QS patterns, sinoatrial
blocks, atrioventricular blocks, and left bundle-
branch blocks. These abnormalities were more
frequent in the neurologically severe group (Table
3). Significant prolongations of pre-
ejection period (PEP) and significant reductions of ET/PEP were
also more predominant in the severe group.
Fig. 1 Case 1 in the affected group shows an abnormal systolic wave with late systolic bulge (B) in the apex cardiogram and a mid-systolic click (K) on phonocardiogram. ACG, apex cardiogram; CAP, carotid arterial pulse; JVP, jugular venous pulse; PCG, phonocardiogram.
Cardiovascular function in amyloid polyneuropathy

Fig. 2 Case 2 in the affected group shows complete atrioventricular block, a QS pattern in II, III, aVF, V1-5, left axis deviation, left bundle-branch block, and distinct ST-T changes.

Fig. 3 Case 3 in the affected group reveals sinoatrial block, a ventricular premature beat, a QS pattern in V1-3, left axis deviation, and left bundle-branch block.

Fig. 4 Case 5 in the non-affected group shows first degree atrioventricular block, low voltage in limb leads, left axis deviation, and a QS pattern in V1-3.
The electrocardiograms of the non-affected group (with the exception of those cases having diabetes mellitus and hypertension) were abnormal in only one individual. In the non-affected group the left ventricular systolic time interval was normal.

Representative electrocardiographic abnormalities are illustrated in Figs 2 to 4.

Discussion

Cardiac involvement has been variably emphasised in previous reports of familial amyloid polyneuropathy. Frederiksen et al. (1962) found that congestive heart failure was often present when neurological symptoms were minimal. In the 3 cases reported by Allenworth et al. (1969), atrial standstill was noted but heart failure was not evident. Recently, Coelho and Pimentel (1961) in Portugal reported 34 cases of familial amyloid neuropathy of a special type. These cases showed distinct neuropathy but no cardiac symptoms. There were no pronounced changes in heart sounds, and all patients were in sinus rhythm. Only 20 of the cases showed abnormalities in the electrocardiogram, including premature beats, right and left ventricular hypertrophy, incomplete atrioventricular block, bundle-branch block, and non-specific T wave abnormalities. In the 4 cases with familial neuropathy reported by Buja et al. (1970), 1 had heart failure while 3 showed low voltage in the electrocardiogram.

These and other previous reports have suggested that various familial groups with amyloidosis may present quite different clinical syndromes, depending on the predilection for amyloid deposition in the nervous, cardiovascular, or renal systems, or in the conduction system vs. the general musculature of the heart. A similarity has been reported, in this regard, between the cases with familial amyloid neuropathy in Portugal and those in Japan (Andrade et al., 1970). However, in the Japanese cases, the degree of cardiac dysfunction closely paralleled the severity of the neurological disorder, and a wide variety of electrocardiographic abnormalities were encountered, including infarction patterns, sinoatrial and atrioventricular conduction disturbances, left bundle-branch block, tachyarrhythmias, and non-specific ST-T abnormalities. Two of the patients with conduction disturbances (1 sinoatrial and 1 atrioventricular block) required permanent pacemakers because of syncopal attacks. Orthostatic hypotension was associated with severe cardiac dysfunction in 4 of our cases, though Buja et al. (1970) have pointed out that this relation is not consistent.

We have not found a full report of polygraphic findings in familial amyloid neuropathy. In our cases, an abnormal systolic wave was found in the apex cardiogram in 6 of 12 cases of the affected group (in 5 of the 7 severe cases). This abnormality has previously been reported predominantly in patients with ischaemic heart disease and cardiomyopathy (Benchimol, 1977). A prominent systolic murmur was recorded in 4 phonocardiograms and a mid-systolic click in 6 tracings. These findings may be related to papillary muscle dysfunction (Barlow et al., 1968) because it is pertinent that half of the patients with extensive amyloid deposits in papillary muscles at necropsy had apical systolic murmurs (Buja et al., 1970).

The left ventricular systolic time interval was abnormal in 8 of the 12 cases of our affected group. These abnormalities may have been, partly, the result of conduction abnormalities, but they strongly suggested primary myocardial involvement in view of their usually close relation to ventricular performance (Weissler et al., 1968), and the frequently abnormal values found in other types of cardiomyopathy (Benchimol, 1977).

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References


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