Treatment by Pacemaker in Familial Amyloid Polyneuropathy

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Amyloid deposits often involve the heart and cause disturbances in conduction and impulse formation in patients with familial amyloid polyneuropathy (FAP). Seven patients with FAP required pacemaker treatment during eight years. The most frequent bradyarrhythmias requiring pacing were sinus node dysfunction with junctional failure. Our seven patients had attacks and symptoms of bradyarrhythmias. A pacemaker relieved symptoms of bradyarrhythmias with recurrence of dislocation of electrode, exit block, and relatively high threshold. However, pacing did not improve the ultimate prognosis of FAP, because of progressive inanition of FAP. In our series, pacing should have been started earlier before advanced stage according to the ECG findings as in other diseases with bradycardias.

(F. Chest 1999; 96:50-54)

ST = sinus tachycardia; SB = sinus bradycardia; JER = junctional escape rhythm; JEB = junctional escape beat; VER = ventricular escape rhythm; AF = atrial flutter; A = atrial fibrillation; IVC = intraventricular conduction defect; PIA = interval between pacemaker impulse and A wave of His bundle electrocardiogram; HBE = His bundle electrocardiogram

Familial amyloid polyneuropathy is inherited in an autosomal mode and the amyloid deposits involve motor, sensory and autonomic nervous systems. Familial amyloid polyneuropathy is a progressive disease with gradual deterioration, and the prognosis of this disease is grave.

In a small number of patients with this disease, the heart is widely involved by amyloid infiltration, which causes disturbances in impulse formation and in conduction, requiring pacemaker treatment. The condition is found in limited areas in the world. Many reports have been from Portugal and Sweden. It has also been found in localized areas in Japan. Ogawa Village, Nagano, is one of the regions of concentration of this disease in Japan.

In this report, we describe clinical features and ECG abnormalities that required pacemaker treatment, findings of atrial pacing tests, His bundle electrocardiography and pacemaker implantation, and complications in pacemaker treatment in patients with FAP from Ogawa Village, Nagano, Japan.

**Patients and Methods**

Between February 1979 and October 1987, we examined 88 patients with FAP originating from Ogawa Village, Nagano, Japan. Seven of these patients developed symptomatic bradyarrhythmias. They were from five of 34 pedigrees which have been reported previously by Kito et al. All patients suffered from polyneuropathy and showed characteristic clinical manifestations with progressive polyneuropathy. These patients had episodes of syncope or Adams-Stokes' attacks from bradyarrhythmias, but none of these patients had a history of myocardial infarction or any other heart diseases and were not receiving antiarrhythmic medications.

Presence of amyloid was confirmed by sural nerve biopsy in these seven patients. The previously recorded ECGs and rhythm strips were collected and analyzed. Twelve-lead ECGs and bedside monitorings were recorded at various times in all patients. Holter ECG recordings were made in two cases.

Atrial pacing tests were performed in three patients and His bundle electrocardiography (HBE) was recorded in five patients during temporary pacing. At the same time, an endocardial biopsy was done in five patients.

Pacemakers were implanted transvenously after temporary pacing in all seven patients. The clinical features of the seven patients and analysis of 244 ECG recordings including the 12-lead ECGs, Holter ECG recordings, and bedside monitor recordings are presented in this report. Data from atrial pacing tests, HBE and pacemaker implantation, and results of endocardial biopsy are also presented.

**Results**

The patients were two men and five women aged 38 to 49 years old (mean 40). The onset of disease occurred at 29 to 41 years old (mean 35). The duration of affection to the time of pacemaker implantation was 72 to 132 months (mean 104) (Table 1). The retrograde investigation of family trees revealed more than one family member affected with FAP in each family.

**Clinical Features**

The initial symptoms began in the lower extremities with progressive loss of sensation, weakness, superificial dullness, and pain. The subsequent signs and symptoms were muscular atrophy, flaccid paralysis,
trophic disturbances of skin (bull formation and ulceration of skin), sensory dullness in the front chest, loss of weight, malnutrition, and emaciation in all patients. Various manifestations in the autonomic nervous systems were noted in all patients. These included urinary bladder and sphincter dysfunctions, impotence, nausea and vomiting, diarrhea and constipation, and orthostatic hypotension. All seven patients suffered from characteristic progressive familial amyloid polyneuropathy and were bedridden due to muscle weakness.

Five patients had Adams-Stokes' attacks and two patients had syncopal attacks from bradyarrhythmias. Dizziness from orthostatic hypotension was noted in five patients (Table 1).

**ECG Findings**

Twelve-lead ECG revealed minimal R progression with deep S wave in the right precordial lead and small R progression in the left precordial lead. Various disturbances in impulse formation and conduction was observed in all cases (Table 2).

Six patients had bradycardias with episodes of sinus bradycardias or sinoatrial block. One patient had atrial fibrillation with slow ventricular response. All patients eventually developed long phases of sustained junctional escape rhythm. In one case, asystole for eight seconds was recorded via Holter recording. Atrial flutter was noted in one case. Paroxysmal atrial tachycardia, premature atrial contractions and junctional tachycardia with retrograde atrial conduction were seen in case 6. Ventricular escape rhythm or ventricular tachycardia was noted in two cases (case 2 and 6). Premature ventricular beats were seen in two cases. There was a low incidence of beats or rhythm of ventricular origin. A 1st atrioventricular block was seen in three cases.

Atrioventricular dissociation occurred in two cases. In one case left anterior hemiblock and intermittent left bundle branch block was noted. Intermittent right bundle branch block was found in another case. All patients eventually developed an intraventricular conduction defect. None of the seven patients developed complete heart block or advanced block (Table 2).

**Table 1—Clinical Features**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Duration of Affection (months)</th>
<th>Clinical Features</th>
<th>Symptom of orthostatic hypotension</th>
<th>Symptoms of Bradyarrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42 M</td>
<td>72</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Adams-Stokes' attacks, syncope</td>
</tr>
<tr>
<td>2</td>
<td>38 M</td>
<td>132</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Adams-Stokes' attacks</td>
</tr>
<tr>
<td>3</td>
<td>38 F</td>
<td>120</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Adams-Stokes' attacks</td>
</tr>
<tr>
<td>4</td>
<td>49 F</td>
<td>101</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Syncope</td>
</tr>
<tr>
<td>5</td>
<td>42 F</td>
<td>96</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Adams-Stokes' attacks</td>
</tr>
<tr>
<td>6</td>
<td>34 F</td>
<td>78</td>
<td>Polyneuropathy</td>
<td></td>
<td>Syncope</td>
</tr>
<tr>
<td>7</td>
<td>38 F</td>
<td>132</td>
<td>Polyneuropathy</td>
<td>Dizziness</td>
<td>Adams-Stokes' attacks, syncope</td>
</tr>
</tbody>
</table>

In one case left anterior hemiblock and intermittent left bundle branch block was noted. Intermittent right bundle branch block was found in another case. All patients eventually developed an intraventricular conduction defect. None of the seven patients developed complete heart block or advanced block (Table 2).

**His Bundle Electrocardiography and Atrial Pacing Test**

The HBE was recorded in three cases while in sinus rhythm and in one case in junctional rhythm. The AH interval was prolonged in two cases and the HV interval was prolonged in three cases. His bundle rhythm was confirmed by HBE in one case. Right atrial pacing was performed in three cases. The atrioventricular response remained of the 1:1 type up to a heart rate of 150 beats per minute in two cases and up to a heart rate of 90 beats per minute in one case. Sinus node recovery time (SRT) was measured in two cases during sinus rhythm at an atrial pacing rate of 150 beats per minute for three minutes. The SRT was 880 ms and 830 ms, respectively. In the one case, while in His bundle rhythm, escape rhythm recovery time was measured at the atrial pacing rate of 80 beats per minute for three minutes, which revealed a 12,110 ms. In this case, at atrial pacing, the interval between pacemaker impulse and A wave was markedly prolonged. Repeated incremental atrial pacing revealed rate-dependent prolongation of the AH interval. However, the HV interval was prolonged and constant with no connection to pacing rate. The threshold of atrial pacing in this case was 20 mA. The M-mode echocardiogram revealed absence of the A wave of the mitral valve. These findings suggested this was atrial standstill (Table 2).
Table 2—Electrocardiographic and Electrophysiologic Features

<table>
<thead>
<tr>
<th>Case</th>
<th>Nomotopic and its variant</th>
<th>Ectopic rhythm</th>
<th>Disturbances in impulse formation</th>
<th>Disturbances in impulse conduction</th>
<th>Atrial pacing tests and HBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>JER</td>
<td></td>
<td></td>
<td>IVCD</td>
<td>A-V dissociation</td>
</tr>
<tr>
<td>2</td>
<td>ST, SB</td>
<td>JER, JEB, VER, idioventricular rhythm, asystole for 8 second</td>
<td>I'A-V block, SA block, IVCD, intermittent RBBB</td>
<td>PA:32, AH:96, HV:112</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ST, SB</td>
<td>AF, JEB, JER</td>
<td></td>
<td>I'A-V block, SA block, IVCD, A-V dissociation</td>
<td>PA:16, AH:144, HV:56</td>
</tr>
<tr>
<td>4</td>
<td>SB</td>
<td>AF with slow ventricular response</td>
<td></td>
<td>IVCD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SB, ST</td>
<td>JEB, JER, PVC</td>
<td></td>
<td>I'A-V block, SA block, LAHB, intermittent LBBB, IVCD</td>
<td>PA:24, AH:88, HV:92</td>
</tr>
<tr>
<td>6</td>
<td>ST, SB</td>
<td>PAT, PVC, PAC, VT, JER, JEB, junctional tachycardia, VER, ectopic P</td>
<td></td>
<td>IVCD</td>
<td>PA:24, AH:88, HV:40</td>
</tr>
<tr>
<td>7</td>
<td>SB</td>
<td>JEB, JER</td>
<td></td>
<td>IVCD</td>
<td>H:24, HV:88, atrial pacing (threshold:20 mA)</td>
</tr>
</tbody>
</table>

ST: sinus tachycardia; SB: sinus bradycardia; JER: junctional escape rhythm; JEB: junctional escape beat; VER: ventricular escape rhythm; AF: atrial flutter; AF: atrial fibrillation; IVCD: intraventricular conduction defect; LAHB: left anterior hemiblock; PI-A: interval between pacemaker impulse and A wave of His bundle electrocardiogram; HBE: His bundle electrocardiogram.

Endomyocardial Biopsy

Endomyocardial biopsy at right ventricular apex was performed in five patients (cases 2, 4, 5, 6, 7) during temporary pacing. The histologic alteration was variable from case to case. There were variable amyloid deposits in the endocardium. In the subendocardial region, cardiac muscle fibers were partially replaced by degenerated and/or atrophic tissue and scar tissue with amyloid deposits.

Treatment

Pacemakers were implanted in the seven patients after temporary pacing. An endocardial lead was used in four cases. In one case, dislocation of the electrode occurred one month after insertion of the pacemaker. Exit block occurred in the same case after repositioning the endocardial lead. After the experience, a screw-in lead was employed in the remaining three cases.

The pacing threshold with endocardial lead and with screw-in lead were 0.5 to 1.9 mA (0.5 to 1.2 mA, mean 1.4) and 0.3 to 1.2 mA (mean 0.7), respectively. There were no complications in wound healing or with systemic infection in our series, though our patients were in the advanced stage (Table 3). None of our patients had pacemaker syndrome or acute deterioration after pacemaker implantation due to improper pacing rate.

Follow-up

All patients in our series were relieved of symptoms of bradycardias. Pacing did not improve dizziness from orthostatic hypotension. In our cases, pacing did not change the ultimate prognosis of FAP. The survival duration was 10 to 31 months (mean 20). Six patients died from progressive inanition of FAP (pneumonia, urinary infection, sepsis, and malnutrition). One patient was alive for 31 months after insertion of pacemaker (Table 3).

Discussion

Amyloid deposits involve the heart and cause various types of disturbances in conduction and impulse.
function in a limited number of patients with FAP. It has been a subject of controversy whether or not amyloid infiltration of the conduction system accounts for the frequently associated electrocardiographic abnormalities.

Lumb and Schacklett described two cases of sudden death, with extreme amyloid deposition present in the conduction system. James reported direct amyloid deposition in the conduction system in five patients with cardiac amyloidosis with arrhythmias and conduction disturbances.

Buja et al reported that in the five of eight patients with conduction disturbances and arrhythmias, the conduction system contained amyloid deposits, and in the other three patients, no amyloid infiltration was noted in the conduction system.

Ridorfi et al reported only three of the 23 patients with cardiac amyloid deposition in their study contained amyloid deposits within the conduction system. They concluded that direct amyloid infiltration did not account for the majority of arrhythmias and conduction disturbances.

James and Rossi suggested the autonomic nerves in the heart had a close relation to conduction disturbances and arrhythmias. Amyloid deposits were found in the intracardiac nerves in a Portuguese patient with FAP.

Erikson et al suggested, in Swedish cases with FAP, direct amyloid infiltration of the atrioventricular conduction system accounts for the majority of the electrocardiographic disturbances.

In the Japanese patients with FAP, involvement of the intracardiac autonomic nerves and ganglia, as well as conduction system, especially the sinus node, appear to be the common, and the main pathogenesis of arrhythmias and conduction disturbances were sinus bradycardias or sinoatrial block, sinus arrest with sustained functional escape beats and rhythm.

Sinus node failure with junctional dysfunction were important findings that required pacemaker treatment in our patients. Intraventricular conduction defects, absence of advanced block, and low incidence of typical bundle branch block and hemiblock were other findings of electrocardiographic features in our series. The ECG findings and arrhythmias in our patients were similar to those in the Portuguese cases.

In the Swedish cases, the incidence of advanced block and the age distribution were higher than those of our patients. The differences in age distribution between the Swedish cases and our cases makes it difficult to compare directly arrhythmias and conduction disturbances. Even in patients with FAP, pacing should be performed according to ECG findings, symptoms presented, and/or as in other diseases with bradyarrhythmias.

Our patients were in an advanced stage considering the clinical signs and symptoms, duration of affection, and ECG findings. Our patients often had no symptoms or complaints from bradyarrhythmias until they were beset with Adams-Stokes' seizures, because they were confined to bed from muscle weakness. We think the time of pacemaker implantation was delayed in our cases, and pacing should have been done much earlier before episodes of Adams-Stokes' attacks occurred.

Erikson and Olofsson reported pacing may be required at any stage after the onset of polyneuropathy and at any stage of the disease with the exception of the very early stage. Pacemaker insertion, even in the early stage, might be indicated in a limited number of FAP patients. This would be when intermittent progression of sinoatrial block and/or junctional escape rhythm or beats are observed on the ECG findings. The natural course of FAP is progressive in both general condition and arrhythmias. However, the frequency of developing bradyarrhythmias requiring

<table>
<thead>
<tr>
<th>Case</th>
<th>Threshold (mA)</th>
<th>Endocardial voltage (mV)</th>
<th>Electrode</th>
<th>Survival Duration (months)</th>
<th>Complication</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>4.0</td>
<td>Endocard</td>
<td>Dead, 15</td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>14.5</td>
<td>Endocard</td>
<td>Dead, 18</td>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>5.6</td>
<td>Screw-in</td>
<td>Alive, 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.9</td>
<td>5.5</td>
<td>Endocard</td>
<td>Dead, 16</td>
<td>Dislocation of electrode after one month, exit block</td>
<td>Urinary infection</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>5.0</td>
<td>Endocard</td>
<td>Dead, 24</td>
<td></td>
<td>Inanition from polyneuropathy</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>10.5</td>
<td>Screw-in</td>
<td>Dead, 28</td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>5.6</td>
<td>Screw-in</td>
<td>Dead, 10</td>
<td></td>
<td>Inanition from polyneuropathy</td>
</tr>
</tbody>
</table>
pacemaker treatment is low among our FAP patients.
In our series, one dislocation of the electrode occurred one month after pacemaker insertion. Exit block occurred in the same case after repositioning the electrode. In our experience, dislocation of the electrode occurred immediately or within a few days after pacemaker insertion. The relatively long interval after pacemaker insertion to the time of dislocation in this case suggested blocking of capture by the electrode at the endocardium from amyloid deposits. We think loss of capture due to dislocation of an electrode in this case might be caused not by technical failure, but rather by amyloid deposits. Exit block and relatively high threshold in our series also might have resulted from deposits in the endocardium. In our five cases, biopsy revealed amyloid deposits in the endocardium. In Erikson's series, cases with dislocation of the electrode were reported. However, the cause of the dislocation is not certain in his series. After the experience of a case with dislocation of the electrode and exit block, we employed screw-in leads. Since then, we have had no cases of dislocation or exit block. The threshold in cases where an endocardial electrode was used seemed to be higher than that in cases where a screw-in lead was used. However, patients with screw-in leads were small in number and survival duration after implantation of the pacemaker was short, and thus, the efficacy of the screw-in lead was not certain.

Though our cases were in the advanced stage and their general condition had deteriorated, we had no cases with systemic or wound infection after pacemaker implantation. It has been reported that in a case of low compliant myocardium with systemic amyloidosis, an improper pacing rate might have caused acute deterioration after pacing. In our series, none of our patients had acute deterioration or pacemaker syndrome after pacemaker implantation. In Erikson's patients, pacing promptly relieved symptoms from bradyarrdias and made general anesthesia and abdominal surgery possible. In our series also, pacing relieved Adams-Stokes' attacks or syncope from bradyarrdias. However, pacing did not improve the ultimate prognosis of this disease, and the survival duration after pacemaker treatment was short, because progressive inanition was present due to FAP. None of our patients died from cardiac causes, rather our patients died from noncardiac causes related to neuropathy.

In conclusion pacing should have been instituted before reaching the advanced stage according to the ECG findings as in other diseases with bradyarrdias. Pacing relieved Adams-Stokes' attacks or symptoms from bradyarrdias in spite of recurrent dislocation, exit block and relatively high thresholds. However, pacing did not improve the ultimate prognosis of FAP.

ACKNOWLEDGMENT: The authors wish to thank A. J. Arends for help in correcting English. Technical assistance was provided by Hiromi Shioneri.

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