Three-Year Follow-Up of Patients With Right Bundle Branch Block and ST Segment Elevation in the Right Precordial Leads

Japanese Registry of Brugada Syndrome

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OBJECTIVES
We sought to determine the prevalence of right bundle branch block (RBBB) and ST segment elevation in the working Japanese population, as well as the event rate during a three-year prospective follow-up period.

BACKGROUND
A poor prognosis of RBBB and ST segment elevation has been reported in Europe and South America, even in asymptomatic patients; however, a large population of asymptomatic patients with sporadic RBBB and ST segment elevation has not been studied.

METHODS
Ten thousand 12-lead electrocardiograms (ECGs) were obtained during annual check-ups of working adults in the Tokyo area. This three-year prospective follow-up study consisted of 105 patients, including 20 with ventricular fibrillation, 18 with syncope and 67 who were asymptomatic. They were registered from 46 institutions in Japan.

RESULTS
The prevalence of ECG abnormalities in working adults was 0.16%. A coved-type ST segment elevation was related to a history of cardiac events, and 18% of registered patients had PR prolongation and 9.5% had left-axis deviation. The cumulative cardiac event-free rate was 67.6% in the symptomatic group and 93.4% in the asymptomatic group (p = 0.0004) after three years.

CONCLUSIONS
The recurrence rate of cardiac events in symptomatic patients was similar to that reported previously, but it was very low in sporadic asymptomatic patients. The ECG findings may help us to select patients for further examination and more accurate evaluation of their prognoses. (J Am Coll Cardiol 2001;37:1916–20) © 2001 by the American College of Cardiology

Brugada and Brugada (1) first reported a unique electrocardiographic (ECG) syndrome in which ventricular fibrillation (VF) could occur without obvious structural heart disease. Their report drew attention to this condition, and Brugada syndrome has subsequently been recognized in virtually all parts of the world (2,3), although its incidence and distribution remain unclear. We previously reported on the clinical characteristics of 63 Japanese patients who had ECG evidence of right bundle branch block (RBBB) associated with ST segment elevation in the right precordial leads (4). At that time, we determined the incidence of cardiac events in these patients. Subsequently, we continued to enroll new patients and conducted a three-year follow-up study. In addition, to elucidate the incidence of the unique Brugada-type ECG pattern in working Japanese adults, we reviewed 10,000 consecutive ECGs.

METHODS
To determine the prevalence of RBBB associated with ST segment elevation in working Japanese adults, 10,000 consecutive standard 12-lead ECGs were obtained at the annual medical check-ups of the personnel of an electrical company and a pharmaceutical company in the Tokyo area. The age of the employees undergoing assessment ranged from 20 to 66 years (mean 42 ± 9); there were 8,913 men and 1,087 women. The ECGs were reviewed by two cardiologists simultaneously, and if they did not agree, the diagnosis was not accepted.

Electrocardiographic definitions. Complete RBBB was defined as a QRS duration ≥0.12 s, with an RsR$^9$ configuration; incomplete RBBB was defined as a QRS duration ≥0.10 s, with an rSr$^9$ configuration in the right precordial leads. ST segment elevation was defined as high take-off elevation of the J point of at least 0.1 mV in leads $V_1$ to $V_3$.

Registration and follow-up. Prospective follow-up of patients with RBBB and ST segment elevation in the right precordial leads was initiated in April 1994. Information was recorded on designated forms that contained demographic, ECG, historical and therapeutic data. The ECGs were obtained from all patients at the time of registration. Patients qualified for registration if the elevated ST segments had a coved or saddle-back shape (4). The patients were classified into the following three groups: the VF
group, with a history of documented VF; the syncope group, with one or more syncopal attacks; and the asymptomatic group, with neither VF nor syncope.

For each patient enrolled in this study, prospective follow-up was performed, and the following information was recorded at each review: any recurrence of syncopal attacks; the cause of death, if this occurred during follow-up; and a 12-lead ECG. Follow-up information was obtained for all patients every six months after registration.

From April 1994 to the end of December 1995, 129 patients were registered at the registration center (First Department of Internal Medicine, Nippon Medical School, Tokyo). The patients were enrolled from 46 institutions in Japan (see Appendix). All of them underwent a physical examination, chest radiography, 12-lead electrocardiography and M-mode or two-dimensional echocardiography. All of the ECGs were reviewed by two investigators, and 24 patients were excluded from follow-up because ST segment elevation was not obvious in the right precordial leads or because they had other heart diseases, or both. Thus, 105 patients were enrolled for follow-up. Upon physical examination and echocardiography, none of these patients were enrolled for three-year follow-up. Upon physical examination and echocardiography, none of these patients had any obvious underlying heart disease. There was no evidence of electrolyte abnormalities in any of the patients at registration.

Statistical analysis. All data are expressed as the mean value ± standard deviation. A frequency comparison was performed by using the chi-square test with Yates’ correction. A two-tailed p value < 0.05 was considered to indicate significance. The probabilities of survival and event-free survival were estimated by the Kaplan-Meier method, and the significance of differences was calculated by using the log-rank test.

<table>
<thead>
<tr>
<th>Type of ST Segment Elevation</th>
<th>VF Group (n = 20)</th>
<th>Syncope Group (n = 18)</th>
<th>Asymptomatic Group (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41 ± 10</td>
<td>47 ± 13</td>
<td>45 ± 14</td>
</tr>
<tr>
<td>Men</td>
<td>20</td>
<td>17</td>
<td>62</td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Type of ST segment elevation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coved type</td>
<td>17</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Saddle-back type</td>
<td>3</td>
<td>7</td>
<td>41</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number of patients. VF = ventricular fibrillation.

RESULTS

Prevalence of ECG abnormalities. Among the 10,000 working adults, a total of 243 (2.4%; 235 men and 8 women) had incomplete RBBB, and 77 (0.77%; 73 men and 4 women) had complete RBBB. Only 16 men (0.16%), and none of the women, had obvious ST segment elevation in the right precordial leads. Five of the men were registered for follow-up, but the other 11 did not agree to enter the study. None of the subjects with complete RBBB had ST segment elevation in the right precordial leads (Table 1).

Clinical and ECG characteristics. The clinical features and the pattern of ST segment elevation in the right precordial leads of the 105 patients (average age 45 ± 13 years) enrolled for follow-up are presented in Table 2. There were only six women: one in the syncope group and five in the asymptomatic group. At the time of registration, coved-type ST segment elevation was more frequently observed in the VF group (85%) and in the syncpe group (61.1%) than in the asymptomatic group (38.8%). Five of the 105 subjects had a family history of sudden death (SD). These deaths include the cousin of a 38-year-old man in the VF group, the twin sibling of a 48-year-old man in the syncope group and the sibling of a 69-year-old man in the asymptomatic group.

Twenty patients had at least one episode of documented VF before registration, and 18 had at least one episode of syncope, whereas the remaining 67 asymptomatic subjects had experienced neither VF nor syncope. Their age distribution showed a peak in the early 50s, with the majority of

Table 1. Frequency of Right Bundle Branch Block and ST Segment Elevation in the Right Precordial Leads (V₁ to V₃) in a Japanese Working Population in the Tokyo Metropolitan Area

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. of ECGs</th>
<th>Complete RBBB</th>
<th>Incomplete RBBB</th>
<th>Incomplete RBBB and ST Segment Elevation in Leads V₁ to V₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Men Women</td>
<td>n Men Women</td>
<td>n Men Women</td>
<td>n Men Women</td>
</tr>
<tr>
<td>20–29</td>
<td>1,145 718 427</td>
<td>4 2 2</td>
<td>14 12 2</td>
<td>1 1 0</td>
</tr>
<tr>
<td>30–39</td>
<td>2,109 1,890 219</td>
<td>9 9 0</td>
<td>49 48 1</td>
<td>6 6 0</td>
</tr>
<tr>
<td>40–49</td>
<td>4,778 4,462 316</td>
<td>40 39 1</td>
<td>116 114 2</td>
<td>6 6 0</td>
</tr>
<tr>
<td>50–59</td>
<td>1,919 1,799 120</td>
<td>24 23 1</td>
<td>64 61 3</td>
<td>3 3 0</td>
</tr>
<tr>
<td>60–69</td>
<td>49 44 5</td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Total</td>
<td>10,000 8,913 1,087</td>
<td>77 73 4</td>
<td>243 235 8</td>
<td>16 16 0</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; RBBB = right bundle branch block.
the patients in their late 30s to early 60s. Symptomatic patients with at least one cardiac event (VF or syncope) were most frequently in their late 40s, whereas a large majority of the patients without any cardiac events were in their 50s to early 60s (Fig. 1).

On the 12-lead ECG, all 105 registered patients had RBBB and ST segment elevation of 0.1 mV in leads V1 to V3. At registration, 54 ECGs (51.4%) showed coved-type ST segment elevation, and the remaining 51 ECGs showed saddle-back ST segment elevation. Coved-type ST segment elevation was most frequent in the VF group (85%), but was still seen in 38.8% of the asymptomatic group. When the patients were classified into two groups, the frequency of the coved type was significantly higher in the symptomatic group than in the asymptomatic group (p = 0.0001). On the ECG, 18.1% also had PR prolongation (PR interval ≥0.22 s), and 9.5% had left-axis deviation (a frontal plane QRS axis between −30° to −90°). These findings were more frequent in patients with a history of cardiac events, but the differences were not statistically significant (Table 3).

**Follow-up data.** During the three-year follow-up, nine patients dropped out and did not visit the hospital for review. All nine patients were asymptomatic at the time of registration, with an abnormal ECG detected incidentally at their annual medical check-ups. During the three-year follow-up, a total five patients died: two patients in the VF group died suddenly; two asymptomatic patients died of cancer; and one asymptomatic patient died of an unknown cause. Seven patients had placement of an implantable cardioverter-defibrillator (ICD) because of the recurrence of VF, or because of new VF in one asymptomatic patient. Figure 2 shows the Kaplan-Meier curves for survival without any cardiac events, including sustained ventricular arrhythmias or syncope. The symptomatic patients are compared with the asymptomatic patients. The cumulative cardiac event-free survival rate was 67.6% in the symptomatic groups and 93.4% in the asymptomatic group (log-rank test; p = 0.0004) after three years. Figure 3 also shows the Kaplan-Meier survival curves for the symptomatic and asymptomatic groups. The survival rates were 74.7% in the symptomatic group and 92.2% in the asymptomatic group (log-rank test; p = 0.017). There was a significantly higher rate of cardiac events and death from all causes in symptomatic patients during the follow-up period.

**DISCUSSION**

It is important to elucidate the prevalence of ECG abnormalities related to Brugada syndrome and to determine the prognosis of these patients. In this study, we investigated the prevalence of Brugada syndrome, as demonstrated by electrocardiography, and we also performed three-year follow-up.

**Prevalence of ECG abnormalities.** The prevalence of complete RBBB is 2.2% and that of incomplete RBBB is 1.7% in patients at a general hospital in Japan (5). These values are comparable to those reported by Katz and Pick (6) (2.3% and 1.1%, respectively). It has also been reported that the population-based prevalence of isolated, complete RBBB was in the range of only 0.18% to 0.35% (7,8).

**Table 3. Electrocardiographic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>n = 105</th>
<th>Coved Type (n = 54 [51.4%])</th>
<th>Saddle-Back Type (n = 51 [48.6%])</th>
<th>PR Prolongation (n = 19 [18.1%])</th>
<th>Left-Axis Deviation (n = 10 [9.5%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic group</td>
<td>38</td>
<td>28 (73.7%)</td>
<td>10 (26.3%)</td>
<td>10 (26.3%)</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>VF</td>
<td>20</td>
<td>17 (85%)</td>
<td>3 (15%)</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>18</td>
<td>11 (61.1%)</td>
<td>7 (38.9%)</td>
<td>5 (27.8%)</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>Asymptomatic group</td>
<td>67</td>
<td>26 (38.8%)</td>
<td>41 (61.2%)</td>
<td>9 (13.4%)</td>
<td>4 (6.0%)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of patients. *VF* = ventricular fibrillation.
Three-year follow-up. The prognosis of Brugada syndrome has been investigated in Europe and South America. Brugada et al. (11) reported a very poor prognosis of this syndrome even in asymptomatic patients. They studied 63 patients with the typical ECG pattern. During a mean follow-up period of 34 months, an arrhythmic event occurred in 34% of the symptomatic patients and in 27% of the asymptomatic patients. In Thailand, sudden unexplained death syndrome, with an accompanying ECG abnormality like Brugada syndrome, also seems to occur at a higher incidence in patients with previous cardiac events (12). Our study demonstrated a lower incidence of arrhythmic events, especially in asymptomatic patients. Among 67 asymptomatic patients, only one patient (1.5%) had an episode of VF and received an ICD during three-year follow-up. In contrast, the symptomatic patients who had a history of VF or syncope developed arrhythmic events far more frequently (25.7%), and their event rate was not much different from that of European patients (11). In our Japanese asymptomatic group, however, the event rate was lower than that of European patients. In the European follow-up study (11), the asymptomatic group included more family members affected with Brugada syndrome, and fewer sporadic patients, than the present study (only two of our patients had a family history of syncope or SD). In our series of asymptomatic patients, the majority of cases were sporadic, and only one of them died suddenly of an unknown cause during the follow-up period. Of course, even one SD in 67 (1.5%) may seem important for physicians. Nearly half a century ago, an ECG abnormality similar to Brugada syndrome was described. Osher and Wolff (13), as well as Edeiken (14), reported ST-segment elevation in young men; the magnitude of the ST segment elevation varied spontaneously and persisted with no cardiovascular events for months or even up to five years. They concluded that this ST segment elevation was not necessarily indicative of myocardial disease, but may represent a normal variant. Since then, many physicians have considered that such ECG findings are a normal variant that does not need further investigation in patients with no obvious cardiovascular abnormalities upon physical examination and echocardiography. In the future, however, we have to follow up these patients more carefully, even if they have no family history of SD or Brugada syndrome.

Conclusions. The present study assessed the prevalence of ECG abnormalities related to Brugada syndrome in working Japanese adults. Also, a prospective three-year study was performed in 105 patients with this condition. The cumulative event-free rate was significantly lower in symptomatic patients than in asymptomatic patients. We concluded that RBBB plus ST segment elevation might be associated with a lower cardiac event rate than previously expected in individuals who have an apparently normal heart, with no family history of SD. However, they should be followed up more carefully than before, when they were considered to be a normal variant. The ECG findings, such as coved-type ST segment elevation, PR prolongation and left-axis deviation, may help us to identify patients for further examination and more accurate evaluation of their prognosis.

APPENDIX

Acknowledgments
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REFERENCES