Clinical and Genetic Heterogeneity of Right Bundle Branch Block and ST-Segment Elevation Syndrome

A Prospective Evaluation of 52 Families

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Background—The ECG pattern of right bundle branch block and ST-segment elevation in leads V1 to V3 (Brugada syndrome) is associated with high risk of sudden death in patients with a normal heart. Current management and prognosis are based on a single study suggesting a high mortality risk within 3 years for symptomatic and asymptomatic patients alike. As a consequence, aggressive management (implantable cardioverter defibrillator) is recommended for both groups.

Methods and Results—Sixty patients (45 males aged 40±15 years) with the typical ECG pattern were clinically evaluated. Events at follow-up were analyzed for patients with at least one episode of aborted sudden death or syncope of unknown origin before recognition of the syndrome (30 symptomatic patients) and for patients without previous history of events (30 asymptomatic patients). Prevalence of mutations of the cardiac sodium channel was 15%, demonstrating genetic heterogeneity. During a mean follow-up of 33±38 months, ventricular fibrillation occurred in 5 (16%) of 30 symptomatic patients and in none of the 30 asymptomatic patients. Programmed electrical stimulation was of limited value in identifying patients at risk (positive predictive value 50%, negative predictive value 46%). Pharmacological challenge with sodium channel blockers was unable to unmask most silent gene carriers (positive predictive value 35%).

Conclusions—At variance with current views, asymptomatic patients are at lower risk for sudden death. Programmed electrical stimulation identifies only a fraction of individuals at risk, and sodium channel blockade fails to unmask most silent gene carriers. This novel evidence mandates a reappraisal of therapeutic management. (Circulation. 2000;102:2509-2515.)

Key Words: heart arrest ■ genetics ■ fibrillation ■ arrhythmia
proposed that asymptomatic patients are at high risk because the "cumulative proportion of VF [ventricular fibrillation] and cardiac arrest occurred in approximately 60% of patients within one year" and because no difference was found between the outcome of symptomatic and asymptomatic individuals. These views underlie the current aggressive management, including programmed electrical stimulation (PES) and implantation of a cardioverter-defibrillator (ICD) in all inducible subjects.

From a large cohort of Brugada syndrome patients, we present data at variance with the current view and propose that in analogy with the long-QT syndrome, the Brugada syndrome is characterized by incomplete penetrance and heterogeneous clinical phenotype (S.G.P., unpublished data, 1999). This information should be incorporated in clinical practice to redefine therapeutic strategies.

Methods

Study Population and Clinical Evaluation

The study population consisted of 52 probands and 100 family members identified in 9 centers. The present study was approved by our Institutional Review Committee, and subjects gave informed consent for clinical and genetic evaluation. The clinical diagnosis of Brugada syndrome was established in 60 subjects. In all patients, the presence of structural heart disease was excluded after extensive evaluation, including blood enzymes and electrolytes (n=60), Holter monitoring (n=60), echocardiogram with careful evaluation of the right ventricle (n=60), stress test (n=45), and nuclear MRI (n=30). Invasive tests included coronary angiography (n=49), electrophysiological study with PES (n=39), and endomyocardial biopsies (n=6). Patients were treated on the basis of the attending physician’s judgment. Genetic analysis and family counseling were performed at the Molecular Cardiology Laboratories of the Maugeri Foundation in Pavia.

Follow-up data were obtained during patients’ visits. An arrhythmic event was defined as a documented episode of syncopal ventricular arrhythmia or sudden death or as an appropriate shock discharged by an ICD. Shocks were defined as “appropriate” on the basis of analysis of stored electrograms.

Mutation Analysis

DNA was extracted from peripheral blood lymphocytes by following standard procedures. Primer pairs for the amplification of SCN5A were used. SSCP analysis was performed on amplified genomic DNA. Samples resulting in mobility shifts were directly sequenced or subcloned into pBlueScript SK− (Stratagene) and sequenced on both strands by use of automatic sequencing.

Statistical Analysis

Data are presented as mean±SD. The event-free analysis was estimated by the Kaplan-Meier method, and the follow-up curves are shown to the point where 20% of the population at risk was still included.

Results

Demographic and Clinical Profile of Patients

Sixty individuals (45 males, mean age 40±15 years) with clinical and ECG diagnosis of Brugada syndrome were identified in 52 families (Table 1). Seventeen (28%) of 60 affected individuals (14 males, mean age 37±16 years) presented with aborted sudden death; 14 of them (82%) had a preceding history of syncopal episodes. Thirteen additional patients (11 males, mean age 44±18 years) had syncopal events. Overall, 30 (25 males) of the 60 patients were symptomatic (mean age 39±16 years, median 41 years), and 30 of 60 patients were asymptomatic (mean age 42±14 years, median 45 years). The Kolmogorov-Smirnov test demonstrated normal distribution of age in both symptomatic and asymptomatic patients. Of the symptomatic patients, 83% were males.

Family History

Family history revealed that 15 victims of sudden death were present in 11 (21%) of 52 families. Victims (10, all males) died at a mean age of 20±17 years (range 2 months to 57 years). Autopsy, available for 7 patients, demonstrated no structural heart disease. In one victim with negative cardiac evaluation who had died suddenly after recurrent syncpe, postmortem diagnosis of Brugada syndrome was established by extracting genomic DNA from a cardiac tissue.

Clinical Evaluation and Treatment

Pharmacological Challenge With Sodium Channel Blockers

Flecainide (2 mg/kg IV) or ajmaline (1 mg/kg IV) was administered as a bolus over 10 minutes in 41 individuals; the ST-segment pattern was worsened (further elevation ≥2 mm) in 17 (41.5%) of the 41 patients, and the appearance of a diagnostic ECG pattern was induced in 18 (44%) of the 41 patients. The test was negative in 6 (14.5%) of the 41 patients (3 symptomatic and 3 asymptomatic).

The reproducibility of a positive test was assessed in 6 patients. A concordant effect on ST-segment elevation was observed in 3 of 6 patients (Figure 1). In 3 patients with an intermittent clinical pattern, the provocative pharmacological test elicited an attenuated ECG pattern (Figure 2).

Electrophysiological Study

PES was performed in 39 (65%) of 60 patients after having obtained informed consent. Similar to the study by Brugada et al., the present study evaluated patients at different sites, and stimulation protocols were not identical: a maximum of 3 ventricular extrastimuli were delivered unless VF was elicited at a previous step.

In 26 (67%) of 39 patients, VF or sustained polymorphic ventricular tachycardia (VT) was induced (Table 2). Of the 26 inducible patients, 13 (50%) were asymptomatic at a mean

<table>
<thead>
<tr>
<th>Clinical Profile</th>
<th>Patients, n (%)</th>
<th>Males, n (%)</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>60/60 (100)</td>
<td>45 (75)</td>
<td>40±15</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>17/60 (28)</td>
<td>14 (82)</td>
<td>37±16</td>
</tr>
<tr>
<td>Syncope</td>
<td>13/60 (22)</td>
<td>11 (85)</td>
<td>44±18</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>30/60 (50)</td>
<td>20 (67)</td>
<td>41±14</td>
</tr>
<tr>
<td>PES inducibility</td>
<td>26/39 (67)</td>
<td>21 (81)</td>
<td>40±13</td>
</tr>
</tbody>
</table>

Genetic characteristics

| Genotyped families | 8/52 (15) | ... | ... |
| Gene carriers      | 28/44 (64)| 16 (57)| 38±19 |
| Silent gene carriers | 20/28 (71)| 12 (60)| 40±20 |

Values are mean±SD for age.
age of 41±14 years, whereas 7 (54%) of 13 noninducible patients were symptomatic. Overall, in this cohort with 30 months of follow-up, the positive predictive value of PES was 50%, and the negative predictive value was 46% (test accuracy 49%). Two of the noninducible patients underwent flecainide administration (2 mg/kg IV) followed by PES. In both patients, rapid polymorphic VT was induced.

Treatment
The treatment of the patients was decided at each individual center. An ICD was implanted in 26 (43%) of 60 patients. In 11, it was implanted because of previous cardiac arrest; in 10, it was implanted on the basis of inducibility with PES (2 with family history of juvenile cardiac arrest); and in 5, it was implanted because of family history of sudden death. Drugs (β-blockers, n=1; sotalol, n=4) were prescribed in 5 of 60 patients (in 1 patient, drugs were in addition to the ICD). Thirty patients remained without therapy (26 asymptomatic and 4 symptomatic subjects who refused treatment).

Clinical Follow-Up
During a mean follow-up of 33±38 months, 5 (8%) of 60 patients experienced a cardiac arrest. All the recurrences occurred in ICD carriers with a previous history of cardiac arrest. Analysis of stored electrograms allowed us to define the nature of the events triggering the shocks (Figure 3, top). None of the 30 asymptomatic patients developed symptoms (syncope, sustained VT, or VF); in 2 of them, ICD interrogation revealed short runs (up to 5 beats) of fast nonsustained VT.

Standard event-free analysis during follow-up was performed (Figure 4A), but we also constructed Kaplan-Meier curves in consideration of the fact that in a genetic disease, risk exposure starts at birth.8 Cases were censored when cardiac arrest occurred in symptomatic patients (n=17). Survival curves show that the risk of events is relatively low before 40 years of age and that it increases substantially thereafter (Figure 4B).

Two patients experienced inappropriate discharges (Figure 3, bottom): a 20-year-old asymptomatic man with a family history of sudden death experienced 3 inappropriate discharges. Successful defibrillation was delivered to 30-year-old man, carrier of mutation R965C, while he was sleeping. Inappropriate discharge occurred in 22-year-old man, carrier of mutation D1114N, during physical exercise and sinus rate of 190 bpm.
charges during physical intense activity and fast sinus rhythm >190 bpm; a 45-year-old man received 32 consecutively delivered inappropriate shocks because of detection of the repolarization wave, precipitated by physical activity and fast rate.

Genetic Analysis

Mutations in the open reading frame of the SCN5A gene were identified in 8 (15%) of 52 probands (5 asymptomatic and 3 symptomatic). None of 400 controls (800 chromosomes) and of 200 long-QT syndrome probands carried the same DNA alterations. The 8 mutations were single residue substitutions leading to an amino acid change and were distributed throughout the protein (Figure 5).

Forty-four family members of 4 genotyped probands accepted genetic screening. The ECG was negative for right bundle branch block and ST-segment elevation in all 44 individuals, and all of them were asymptomatic. Nonetheless, DNA analysis documented a mutation in 20 (45%) of these 44 family members, hereafter defined as silent gene carriers. Mutational uniformity was present among family members; however, a large variability in clinical manifestations was observed. Analysis of clinical manifestations and family history reveal a highly malignant form of the disease associated with the L567Q mutation (Figure 5).

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Sudden Death</th>
<th>Symptomatic Gene Carriers</th>
<th>Asymptomatic Gene Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - V254M</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2 - G219S</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3 - L567Q</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>4 - F892I</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5 - R865C</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>6 - E1052K</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7 - D1114N</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>8 - Y1179H</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 5. Top, SCN5A mutations identified in present study and list of clinical features of gene carrier family members. Bottom, Predicted topology of cardiac sodium channel SCN5A. Numbered labels on schematic drawing correspond to mutation number shown in top panel and indicate position of each mutation within the protein.

Pharmacological Challenge in Gene Carrier Family Members

To define its accuracy, pharmacological challenge with sodium channel blockers was offered to the 20 silent gene carriers (gene-positive relatives) and accepted by 13. The drug challenge unmasked the ECG pattern in only 2 (15%) of these 13 gene carriers. Overall, the drug challenge was concordant with the genetic status only in 6 of 17 subjects (4 of 8 probands and 2 of 13 family members), scoring a positive predictive value of 35%.

Penetrance of Brugada Syndrome

Penetrance was assessed in the 4 genotyped families with a positive baseline ECG in the probands. Because the baseline ECG was negative in all 20 family-member gene carriers, the average penetrance based on ECG analysis was 16% (4 of 24). It was 50%, 25%, 12.5%, and 12.5% in the individual families.

Discussion

The current aggressive clinical management of patients affected by the Brugada syndrome is based on a single prospective study that includes a high proportion of resuscitated cardiac arrest survivors.5 The data in the present study differ from data published by Brugada et al5 and question the alleged high risk of cardiac events within 3 years from diagnosis in asymptomatic individuals and the predictive accuracy of PES. They also show that in a genotyped population, the diagnostic accuracy of pharmacological challenge is lower than previously estimated.5 This novel information should help to reshape therapeutic strategies for the individual patients affected by the Brugada syndrome when both safety and quality of life are considered.

Present Knowledge

The syndrome involving right bundle branch block and ST-segment elevation, or Brugada syndrome, is a cardiac genetic disease manifested by sudden death in individuals with a structurally normal heart. The disease is inherited as an
autosomal dominant trait, and mutations cosegregating with the phenotype have been identified in the SCN5A gene encoding for the cardiac sodium channel. The natural history of the disease has been outlined by Brugada et al through the prospective evaluation of 63 patients followed for \( \approx 3 \) years. Their data showed that the ECG diagnosis of Brugada syndrome is associated with a 27% incidence of syncope or sudden death within a mean follow-up of 34 months and that the probability of sudden death in asymptomatic individuals is not different from that of cardiac arrest survivors. It was on this basis that the current view fostering aggressive therapeutic management was generated.

Based on the same report, 2 procedures have entered clinical practice for the diagnosis and management of patients with the Brugada syndrome. One is the provocative test with sodium channel blockers, proposed to unmask the diagnostic ECG pattern in patients with an apparently normal ECG. The other is PES, used to identify individuals at risk and to guide therapy. Both approaches still await independent validation.

**Clinical Profile of Patients**

We evaluated 60 consecutive patients with the diagnosis of Brugada syndrome to define their clinical and genetic profiles. In agreement with previous observations, the ECG diagnosis was predominant among males (75%), and 80% of the cardiac arrests occurred in males, mainly after the third decade of life. As a novel observation, we also found that major cardiac events may occur also in children and neonates.

**Risk of Sudden Cardiac Death**

Of the patients reported by Brugada et al, 75% had survived cardiac arrest, and several of the remaining individuals were their family members. This raises the possibility that the study of Brugada et al provides prognostic information concerning a selected subset of patients at particularly high risk, and this would justify and explain the severity of the manifestations observed in this population. A referral bias may be present in the initial cohort of patients affected by any newly described disease, inasmuch as the diagnosis is initially made only in the most severe cases. The same phenomenon has happened with the long-QT syndrome. However, because the Brugada syndrome is more and more often diagnosed in asymptomatic individuals, the need for a correct definition of the risk of cardiac arrest in this group is now pressing.

Despite a similar number of patients (60 versus 63) and mean follow-up (33 versus 34 months), significant differences emerge when the outcomes of patients in the present study and in the study of Brugada et al are compared. Although the recurrence rate in patients with history of aborted cardiac arrest is similar (29% versus 32%), the occurrence of events in asymptomatic individuals is strikingly different (0% versus 27%). Overall, our data indicate a very low number of arrhythmic events (0.007 event/y, which is based on 2449 years of observation in 60 patients). Still, aggressive management of these subjects may remain justifiable on the basis of the lethality of the “few” events as shown by the persistence of a life-long risk (Figure 4B). Importantly, if an ICD is implanted, an appropriate therapy might be delivered after only several years. This evidence diverges from that of the previous study, in which one third of asymptomatic patients had their first event within 3 years.

Management strategies of a disease characterized by a low number of highly lethal events should be based on risk stratification algorithms to tailor treatment to the individual risk. PES is largely used to define risk even if words of caution have been raised about its prognostic value. We assessed the value of inducibility during PES and confirmed its limited accuracy (positive predictive value 50%, negative predictive value 46%). Remarkably, PES “missed” 7 symptomatic individuals (4 cardiac arrest survivors). Thus, there is no rationale for justifying a therapeutic decision on the basis of the outcome of PES. The difficult choice to implant or not an ICD in an asymptomatic patient will have to be made independently of PES and should be weighed against the cost in terms of quality of life, taking into account the risk of inappropriate shocks that may be enhanced by the abnormal repolarization. The failure of PES to correctly identify patients at high or low risk should not be surprising in a disease characterized by an intermittently abnormal repolarization, which is probably responsible for an intermittent electrical instability. In such a variable setting, the outcome of PES could simply reflect the degree of electrical stability present when the test is performed, with little bearing on future events.

**Genetic Evaluation of Brugada Syndrome Patients**

Most patients reported in the present study presented as sporadic cases; only a few of them had relatives with ECG diagnosis of the disease or with history of premature unexplained sudden death. On the basis of our experience with the long-QT syndrome, we suspected that incomplete penetrance might be present in Brugada syndrome as well and, therefore, that most of the “sporadic cases” would in fact be members of families with nonpenetrant gene carriers. Genetic analysis revealed mutations in the cardiac sodium channel gene in 8 (15%) of 52 patients, suggesting that other genes are involved in the syndrome (genetic heterogeneity). In 4 of the 8 families with a cardiac sodium gene mutation, we were able to extend clinical and genetic evaluation to the family members of the proband, and we demonstrated the presence of incomplete penetrance, as low as 12.5% in 2 families. At variance with what has previously been reported, pharmacological challenge with flecainide or ajmaline failed to reveal the disease in most gene carriers with a normal ECG.

**Clinical Management of Brugada Syndrome Patients**

The present study shows that the diagnosis of Brugada syndrome may be elusive not only because the ST-segment elevation pattern is intermittent, as previously indicated, but also because the pharmacological challenge with sodium channel blockers has modest reproducibility and may be negative in nonpenetrant gene carriers.
When the diagnosis is suspected, e.g., with a survivor of cardiac arrest without structural heart disease, repeated observations with a 12-lead Holter monitor and repeated provocative tests should be performed before dismissing the diagnosis. Genetic evaluation may be useful in unmasking subclinical forms.

When diagnosis is established, management strategies should be devised, and the data in the present study call for reassessment of the current approach (Figure 6A). Even if we have shown that asymptomatic patients remain as such after a mean follow-up of 3 years, we cannot exclude the possibility that they might develop cardiac arrest at a later time in their life. The innovative information of the present study is the evidence that short-term (3-year) risk of cardiac arrest is low in asymptomatic individuals (irrespective of the outcome of PES) and that it is probably low enough to justify the decision to postpone implantation of an ICD. Management strategies for asymptomatic patients should reflect this evidence.

Two concepts are germane to the development of a novel algorithm for the management of Brugada syndrome patients: (1) PES is not an adequate risk predictor, and (2) self-terminating VT episodes are likely to be present in high-risk patients. The latter statement is based on the evidence that 82% of cardiac arrest survivors had histories of syncope likely to represent self-terminating VT. Furthermore, in 2 asymptomatic patients implanted with an ICD, nonsustained VT episodes (not perceived by the patients) were recorded by the device. Accordingly, we are currently evaluating an alternative strategy for the management of Brugada syndrome patients (Figure 6B). According to the proposed algorithm, symptomatic patients (syncope/cardiac arrest documento VT) and patients with a family history of premature sudden cardiac death would receive an ICD. Asymptomatic patients without family history of sudden death and silent gene carriers would receive an insertable loop recorder, and family members would be trained for providing basic life support and for using an automatic external defibrillator. Compared with presently recommended management (Figure 6A), this novel approach offers a more conservative use of ICDs and a more accurate monitoring of asymptomatic individuals (insertable loop recorders versus periodic clinical evaluation); furthermore, it attempts to improve the success of early resuscitation by implementing a “domestic” chain of survival. Limitations of the proposed approach include sudden death out of home/family surveillance and the constant mental stress to patient and family. If our ongoing evaluation will confirm acceptance of this approach by patients and families, its assessment in a randomized study will become feasible.

Study Limitations
The present study has limitations. The limitations are those commonly present in studies with patients from multiple institutions. They include lack of uniformity in diagnostic procedures, in therapeutic approaches, and in the length of follow-up.

However, it is important to stress that the limitations that we mention for the present report are exactly the same present in the report on which current management is based. Extension of the follow-up period to at least 10 years is required before drawing safe conclusions about natural history, risk of death, and response to therapy in patients with Brugada syndrome.

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References


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