Sudden death in patients and relatives with the syndrome of right bundle branch block, ST segment elevation in the precordial leads $V_1$ to $V_3$ and sudden death

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Background The syndrome with an electrocardiographic pattern of right bundle branch block, ST segment elevation in leads $V_1$ to $V_3$ and sudden death is genetically determined and caused by mutations in the cardiac sodium channel. The inheritance of the disease is autosomal dominant. Sudden death may, however, occur from a variety of causes in relatives and patients with this syndrome.

Patients and Methods Twenty-five Flemish families with this syndrome with a total of 334 members were studied. Affected members were recognized by means of a typical electrocardiogram either occurring spontaneously or after the intravenous administration of antiarrhythmic drugs. Sudden deaths in these families were classified as related or not to the syndrome by analysis of the data at the time of the event, mode of inheritance of the disease, and data provided by survivors.

Results Of the 25 families with the syndrome, 18 were symptomatic (at least one sudden death related to the syndrome) and seven were asymptomatic (no sudden deaths related to the syndrome). In total, there were 42 sudden cardiac deaths (12% incidence). Twenty-four of the 50 affected members (47%) suffered (aborted) sudden death and 18 of the 284 unaffected members (6%). This difference in the incidence of sudden death was statistically significant ($P<0.0001$). Patients with (aborted) sudden death caused by the syndrome were younger than patients with sudden death of other or unclear causes (38 ± 4 years vs 59 ± 3 years respectively, $P=0.0003$).

Conclusions In families at high risk of sudden death because of genetically determined diseases, the main cause of sudden death remains the disease. However, almost the half of sudden deaths are caused by unrelated diseases or are of unclear cause. Accurate classification of the causes of sudden death is mandatory for appropriate analysis of the causes of death when designing preventive treatments.

Key Words: Sudden death, right bundle branch block ST elevation syndrome, ventricular fibrillation, Brugada syndrome, genetics of arrhythmias.

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Figure 1  12-lead electrocardiogram from a young athlete who was resuscitated from almost sudden death caused by a rapid polymorphic ventricular tachycardia. Note the elevation of the ST segment in leads V₁ to V₃ and the right bundle branch blocklike pattern in lead V₁. Paper speed is 25 mm·s⁻¹.
symptoms such as syncope\(^2\text{–}^3\). We recently reported the first three mutations associated with this syndrome\(^4\text{–}^9\). These mutations affect the function of the sodium channel encoded by the gene SCN5A. Both genetic and clinical data confirm that the mode of inheritance of this syndrome is autosomal dominant. The only effective treatment to protect against sudden death is, at present, the implantable cardioverter–defibrillator\(^10\text{–}^13\). In a previous publication\(^14\) we reported the absence of clinical or electrophysiological predictors of the recurrence of the ventricular arrhythmias (or of the first occurrence in asymptomatic carriers). In other genetically determined diseases a family history of sudden death has been frequently found predictive of the occurrence of sudden death\(^15,16\). However, sudden death has many different possible causes and it is not necessarily related to the genetically determined diseases in affected families. In the present study we analyse data on the incidence and cause of sudden death in 25 Flemish families with the syndrome.

**Patients and methods**

A total of 25 families living in the Flemish area of Belgium were included in this prospective study. The 25 families consisted of 334 members (192 men and 142 women). The number of members ranged from two to 47 per family. Age ranged from 6 months to 92 years (mean 52 ± 27 years). There were 18 families with at least one (aborted) sudden death related to the syndrome — symptomatic families — and seven families with no death or other symptoms related to the disease — asymptomatic families. The symptomatic families consisted of a total of 209 members (125 men, 84 women). The asymptomatic families consisted of 125 members (67 men, 58 women; no significant differences in sex distribution between symptomatic and asymptomatic families).

**Identification of affected members**

Two different methods were used to identify affected individuals: (1) a resting electrocardiogram with the pattern typical of the syndrome was considered diagnostic of the disease (Fig. 1); (2) in family members with a normal resting electrocardiogram, ajmaline, flecainide or procainamide were given intravenously under continuous electrocardiographic monitoring. The doses used are given in Table 1. Since the study by Miyazaki and co-workers that we know that these antiarrhythmic drugs may modulate the ST segment elevation in patients with the syndrome\(^17\). We have recently shown that there exists a 100% correlation between phenotype (the electrocardiogram typical of the syndrome, spontaneous or unmasked by drugs) and the genotype (carrier of the genetic defect)\(^18\). Thus, family members showing a typical electrocardiogram after the administration of one of these drugs were considered carriers of the disease. An example is shown in Fig. 2. Informed consent to all parts of this study was obtained from all individuals.

**Classification of the causes of sudden death**

One of the most delicate parts of this study was the classification of causes of sudden death or aborted sudden death. In the syndrome of right bundle branch block and ST elevation, death occurs unexpectedly and without any warning in individuals who feel absolutely fine before the event. Because death is caused by a sudden and rapid polymorphic ventricular arrhythmia, death is instantaneous, and only instantaneous death was considered as possibly related to the disease. Death was considered related to the disease when the ventricular arrhythmias were documented by the treating physicians in a patient with the electrocardiogram typical of the syndrome before or after the event. Affected members had no evidence of any structural heart disease after in-depth cardiological investigation. Sudden death was considered not related to the disease when there was clear evidence for another cause (for instance myocardial infarction) and was considered of unclear cause when the cause was not evident and the mode of inheritance made it unlikely or impossible that the victim suffered from the disease.

**Results**

Of the 334 members, 50 (15%) were determined electrocardiographically before or after the administration of a drug. There were a total of 42 (aborted) sudden deaths, an incidence of 12% for the total population. Twenty-four sudden deaths were related to the disease and occurred, by definition, in affected members. There was thus an incidence of sudden death of almost 50% in affected members. Sudden death had no other cause in affected members. Eighteen sudden deaths occurred in the 284 members without evidence of the disease (an incidence of 6%, \(P<0.0001\) as compared to the incidence of sudden death in affected members). No sudden death could be attributed to the syndrome in non-affected members. Nine sudden deaths were of unclear cause, but the mode of inheritance of the disease made it unlikely

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
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<tr>
<td>Ajmaline</td>
<td>0·7 mg . kg(^{-1}) bodyweight(^{-1}) in 5 min</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg . kg(^{-1}) bodyweight(^{-1}) in 10 min</td>
</tr>
<tr>
<td>Procainamide</td>
<td>10 mg . kg(^{-1}) bodyweight(^{-1}) in 10 min</td>
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that the syndrome was responsible for it. The other nine sudden deaths were caused by myocardial infarction, as assessed from the circumstances of occurrence. Of importance, of the total of 18 sudden deaths not related to the syndrome, 15 occurred in five symptomatic families and three in two asymptomatic families. When we compared data of patients dying suddenly because of the syndrome, to patients dying suddenly without relation to the syndrome, we found no differences in the distribution of sex: 17 of the 24 patients who died because of the syndrome were male, as against 16 of those who died suddenly from other or unclear causes. However, there was a significant difference in terms of mean age: 38 ± 4 years in patients who died in relation to the syndrome vs 59 ± 3 in patients who died unrelated to the syndrome ($P=0.0003$, difference between means 21 ± 4 years, confidence intervals 10 to 32 years).

Of the 18 symptomatic families, seven had a previous history of sudden cardiac death and 11 did not. In all the seven families with a previous history of sudden death, sudden deaths occurred related to the syndrome. However, in five of these seven families sudden death not related to the syndrome also occurred.

Of the seven asymptomatic families, only one had a previous history of sudden death. In this family two sudden cardiac deaths occurred which were unrelated to the syndrome. In one additional asymptomatic family without a previous family history of sudden cardiac

\textbf{Figure 2} 12-lead electrocardiogram of an individual affected by the syndrome but with a normal electrocardiogram under basal conditions. The effects of the administration of 50 mg intravenous ajmaline are shown. Note the appearance of the typical electrocardiogram during the administration of the drug with ST elevation in leads V$_1$ to V$_3$. 
Table 2  Relationship in 25 affected families between a family history of sudden cardiac death and sudden cardiac death related to the syndrome of right bundle branch block, ST segment elevation and sudden death

<table>
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<tr>
<th>Family history of sudden death</th>
<th>Sudden death related to the syndrome</th>
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<tr>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>−</td>
<td>19</td>
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Death, one sudden cardiac death not related to the syndrome occurred during follow-up.

When data from symptomatic and asymptomatic families were considered together, a relationship could not be found between a family history of sudden cardiac death and sudden death related to the syndrome (Table 2). However, a type two error cannot be excluded.

Discussion

This study shows that in families afflicted by hereditary diseases which may result in sudden cardiac death, the exact causes of sudden death have to be carefully studied and classified before giving to each sudden death a mechanistic significance. Of the 42 sudden deaths which occurred in the 25 families affected with the syndrome of right bundle branch block, ST elevation and sudden death, only 24 sudden deaths (57%) were clearly related to the syndrome. The other 43% deaths were either not related to the familial disease, or were of unclear cause. This is important when analysing possible risk factors for sudden death, with the aim of recognizing individual members who may benefit from effective preventive therapies. At present, we still do not know how to identify those individuals affected by the disease who are at the moment asymptomatic, but may become symptomatic in the future[5]. In many other familial diseases a family history of sudden death has been found predictive of further episodes of sudden cardiac death[16]. That was not the case in our study once the exact causes of sudden cardiac death were analysed in a very critical way.

It is not sufficient that a sudden death in a family means that it is related to the disease. Ideally, the exact causes of sudden death must be known. However, as shown in this study, this is not an easy task. Even after careful analysis of the circumstances of death with the survivors and witnesses, nine of 42 sudden deaths (21%) were of unclear cause, and although a myocardial infarction was strongly suspected as cause of death in other nine patients (21%), a definite proof of this diagnosis was not available.

Conclusions

In families affected by an hereditary disease causing sudden death and with an autosomal dominant pattern of transmission, most sudden deaths are related to the disease in affected members. Unaffected members, in contrast may die suddenly because of other diseases. About one-fifth of sudden deaths are of unclear cause and they occur both in symptomatic and asymptomatic families with the syndrome of right bundle branch block, ST segment elevation and sudden death. When assessing risk factors for sudden death in these families, accurate classification of the causes of sudden death is mandatory to avoid overestimation of the prognostic value of a family history of sudden death in families affected by a genetically determined form of sudden death.

References

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