A Population Study of the Natural History of Wolff-Parkinson-White Syndrome in Olmsted County, Minnesota, 1953–1989

Thomas M. Munger, MD; Douglas L. Packer, MD; Stephen C. Hammill, MD; Barry J. Feldman, MD; Kent R. Bailey, PhD; David J. Ballard, MD, PhD; David R. Holmes Jr., MD; and Bernard J. Gersh, MB, ChB, DPhil

Background. Virtually all natural history studies of Wolff-Parkinson-White (WPW) syndrome have been case series and, as such, have been constrained by referral biases, skewed age and sex distributions, or brief follow-up periods. The purpose of our study was to examine the natural history, the development of arrhythmias, and the incidence of sudden death in an entire cohort of pediatric and adult WPW patients from a community-based local population.

Methods and Results. We identified 113 residents of Olmsted County, Minnesota, during the period 1953–1989 using the centralized records-linkage system provided by the Mayo Clinic and the Rochester Epidemiology Program Project. Medical records and ECGs were reviewed to confirm the diagnosis and to establish pathway location by ECG criteria. Follow-up, via record review and telephone interview, was complete in 95% of subjects through 1990. The incidence of newly diagnosed cases was approximately four per 100,000 per year. Preexcitation was not present on the initial ECG of 22% of the cohort. Approximately 50% of the population was asymptomatic at diagnosis, with 30% subsequently having symptoms related to arrhythmia at follow-up. Two sudden cardiac deaths (SCD) occurred over 1,338 patient-years of follow-up, yielding an overall SCD rate of 0.0015 (95% confidence interval, 0.0002–0.0054) per patient-year. No SCD occurred in patients asymptomatic at diagnosis.

Conclusions. The incidence of sudden death in a local community-based population is low and suggests that electrophysiologic testing should not be performed routinely in asymptomatic patients with WPW syndrome. Nevertheless, young, asymptomatic patients, particularly those <40 years old, should return for medical follow-up should symptoms develop. (Circulation 1993;87:866–873)

KEY WORDS • accessory pathways • sudden death • electrocardiography • epidemiology

The earliest reports of sudden cardiac death (SCD) in association with symptomatic Wolff-Parkinson-White (WPW) syndrome appeared in the late 1930s,1,2 several years after the initial description of the syndrome3–6 and Kent's anatomic investigations.7–10 Although the invasive workup of patients with disabling symptoms has seemed clear-cut,11 the approach to the asymptomatic patient with this condition has been more open to question because a subset of often young, asymptomatic patients continue to die unexpectedly (however, the overall risk appears low).12,13 In one large referral group of patients with ventricular fibrillation (VF) and WPW syndrome, >25% had no antecedent symptoms.14

Prior natural history studies15–20 have been plagued by referral biases, inequalities in age and sex distribution, low numbers, or short follow-up periods. Reports of patients with WPW who have been followed for several years to assess the development of symptoms have been lacking.

The purpose of the present study was to examine the development of arrhythmias in asymptomatic WPW patients and the incidence of SCD in an entire cohort of WPW patients from a community-based local population who had been followed for a considerable period of time.

Methods

This investigation was designed as a retrospective incidence cohort study and was organized by use of the centralized records-linkage system provided by the Mayo Clinic and the Rochester Epidemiology Program Project. Together, these two sources provide integrated records of all care delivered at the Mayo Clinic, its two affiliated hospitals (St. Marys and Rochester Method-ist), and at other medical facilities serving the community, including the Olmsted Medical Group and Olm-
sted Community Hospital, as well as other practitioners in the area. These indexes incorporate diagnoses given to outpatients seen in office or clinic situations, emergency room visits, house calls, and nursing homes, as well as those recorded for inpatient care and on death certificates at autopsy. These sources provide information concerning virtually all the primary care delivered for Olmsted County residents.21 Olmsted County individuals who had WPW diagnosed from 1953 through 1989 by a surface ECG were included. All Mayo Clinic, Olmsted County Hospital, and Olmsted Medical Group histories and ECGs were screened by a physician, and patients were required to have an ECG that displayed preexcitation (i.e., a delta wave and anomalous configuration of the QRS complex) for inclusion in the study.

Data collection was complete through 1990 via record review and telephone interview with all available patients or family members. Follow-up was current in 95% of the group. All available ECGs were reviewed by two investigators to confirm the diagnosis, establish the pathway location by surface criteria, and note any changes in the presence of preexcitation over time. Accessory pathway location from the resting surface 12-lead ECG was grouped into five categories: left free wall (LFW), right free wall (RFW), posteroseptal (PS), anteroseptal (AS), and indeterminate.22–24

Data Analysis

The incidence of clinically recognized WPW in Olmsted County, Minnesota, from 1953 through 1989 was calculated from the number of cases observed relative to the total person-years of observation as derived from census data for Olmsted County, Minnesota. Age- and sex-specific WPW syndrome clinical detection rates were calculated similarly. Rates were adjusted to the 1980 US population. Kaplan-Meier survival curves were estimated, and Cox proportional hazards models (using the baseline variables sex, pathway location, age, family history, tachycardia characteristics, symptom frequency, and associated symptoms) were used where appropriate to estimate survivorship in the cohort and to estimate risk for the nonfatal clinical end points of interest. Rates of SCD were reported as deaths per patient-years of follow-up, and 95% confidence intervals (CI) were calculated from a Poisson distribution. Direct comparisons between population means were performed by Student’s t statistic. χ² analysis was used to compare proportions between groups. Differences were tested at a level of p<0.05.

Results

Patient Demographics and Incidence

The cohort of patients totaled 113, including 75 (66%) males and 38 (34%) females. The age at diagnosis ranged from infancy to 77 years (Figure 1). Ten percent of the patients were ≤10 years old at diagnosis. One neonatal patient had prepartum intrauterine tachycardia, was successfully treated with quinidine, and was subsequently diagnosed with WPW immediately after birth. The majority of patients (53%) were in the third and fourth decades of life when diagnosed.

Figure 2 shows incidence data for the diagnosis of WPW per 100,000 persons per year stratified by age. The overall incidence of newly detected WPW in Olmsted County was 3.96 (95% CI, 3.22–4.71) per 100,000 persons per year. The incidence in males (5.47; 95% CI, 4.21–6.73 per 100,000) was twice that for females (2.49; 95% CI, 1.68–3.31 per 100,000). The greatest detection rate of new cases was seen during the first year of life in both males and females, at 20 and six per 100,000, respectively. Secondary peaks occurred later in life, for males in the third decade and for females in the fourth decade.

Only one patient had a first-degree relative with documented WPW. Eight other patients reported family members who had had palpitations or tachycardia. Two patients were married to each other and had three children, none of whom had had a diagnosis of preexcitation.

Associated Cardiac Disease

Seven percent of patients had either dilated cardiomyopathy or congenital heart disease (Table 1). Eight percent had clinically recognized coronary artery disease. WPW was diagnosed in six patients with coronary artery disease during an evaluation for chest pain. Fatal myocardial infarction was responsible for 31% of the 16 total deaths at 59.6±13.5 years old (mean±SD).

ECG Accessory Pathway Location

There was an excess of left-sided versus right-sided locations by surface ECG (LFW, 46%; RFW, 21%; PS, 25%; AS, 2%). Left accessory pathway location was
TABLE 1. Associated Cardiac Disease Among 113 Residents of Olmsted County, Minnesota, Diagnosed With Wolff-Parkinson-White Syndrome, 1953–1989

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease*</td>
<td>4</td>
<td>M</td>
<td>5</td>
<td>Dextrocardia and aortic regurgitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>6</td>
<td>Ventricular and atrial septal defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>Infant</td>
<td>Complete atrioventricular canal, hypoplastic mitral valve ring and left ventricle</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>4†</td>
<td>M</td>
<td>10</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>14</td>
<td>Idiopathic associated with schizophrenia and seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>50</td>
<td>Possible myocarditis</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>9†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All four patients presented in the first year of life with heart failure (not arrhythmia).
†One patient in this group had a combination of two lesions.

more common in males (LFW, 53%; RFW, 15%; PS, 23%; AS, 3%) versus females (LFW, 32%; RFW, 34%; PS, 29%; AS, 0%) \( (\chi^2=4.25, p<0.04) \).

As seen in Figure 3, 88 patients (78%) had a delta wave on their initial ECG. In nine of these patients, preexcitation was abolished as a consequence of WPW surgery. Over a mean follow-up of 18±14 years, nine additional nonsurgical patients had ECGs that permanently normalized.

Twenty-five patients (22%) with no initial preexcitation subsequently were found to have delta waves by surface ECG; the mean time to this group’s first positive ECG was 7±6 years. Overall, these 25 patients did not differ from the entire cohort with respect to surface pathway location (LFW, 44%), sex (68% male), age (mean at diagnosis, 31±23 years), symptomatic status (56% symptomatic at diagnosis), or eventual requirement for surgery (8%). In 10 of these patients (40%) (all nonsurgical), late loss of preexcitation on a subsequent ECG occurred and was persistent; none of these 10 patients were currently using class I or III antiarrhythmic agents. It is conceivable that the late loss of preexcitation in these patients was a rate-related phenomenon or secondary to altered autonomic tone, but no definitive evidence was present for this.

In the entire cohort currently, the delta wave was no longer present on the most recent ECG in 28 patients (25%, nine via WPW surgery and 19 spontaneously). Symptomatic status at present was associated with preexcitation loss (including surgical cases, \( \chi^2=6.55, p<0.02 \); excluding surgical cases, \( \chi^2=3.41, p<0.07 \)). Neither age at diagnosis nor sex was associated with preexcitation loss.

Invasive Cardiac Testing

Eighteen (16%) of 113 patients underwent electrophysiological testing. Indications for invasive evaluation included syncope in five patients, presyncope in six, congestive heart failure (exacerbated by tachycardia) in two, chest pain in one, and recurrent tachycardias despite medical therapy in four. Induced arrhythmias included orthodromic reentrant tachycardia in 12 patients, antidromic reentrant tachycardia in two, atrial fibrillation in 11, and atrial flutter in four.

Of the 11 initially asymptomatic patients who became symptomatic, four underwent electrophysiological study; in this group, arrhythmias induced included atrial fibrillation in four and orthodromic reentrant tachycardia in two. The anterograde accessory pathway refractory period was 340±144 msec, and the shortest RR interval during atrial fibrillation was 275±68 msec. In one patient, the pathway functioned in the anterograde direction only.

Symptomatic Status and Follow-up Results

The total follow-up time for the entire group was 1,338 patient-years (approximately 12 years per patient). Figure 4 shows the subsequent clinical course of all patients, stratified as a function of their symptom status at initial diagnosis.

Symptomatic patients. Sixty patients (53%) were symptomatic at diagnosis: 25 patients experienced limi-
Mortality

A total of 14 nonsudden deaths and two SCDs occurred; five of the nonsudden deaths were due to myocardial infarction (Table 2). Two nonsudden deaths occurred in young patients with cardiomyopathy (patients 3 and 4, Table 2). Patient 3 had a 15-year history of paroxysmal tachycardias and a 1-year history of congestive heart failure. One month before death, he had a cerebrovascular accident and died of a presumed pulmonary embolism and drug toxicity during hospital observation. Autopsy showed a heart weight of 710 g, left ventricular wall thickness of 20 mm, extensive left ventricular myocardial fibrosis, and normal valves, septa, and coronary arteries. Patient 4 had a childhood history of growth retardation, schizophrenia, seizures, and congestive heart failure but no tachycardias. She died during an extended hospitalization of acute hypertension secondary to decompression for dyaminic ileus. Autopsy showed a dilated heart with evidence of ancient myocarditis but normal coronary arteries, septa, and valves; central nervous system degeneration and bilateral bronchopneumonia were also noted.

FIGURE 4. Circle graph showing clinical disposition over a mean follow-up of 11.8 years among 113 residents of Olmsted County, Minnesota, with clinically diagnosed Wolff-Parkinson-White syndrome, 1953–1989, as a function of initial symptom status. Two sudden deaths occurred in the group initially noted to be symptomatic. At latest follow-up, 25% of the symptomatic group had become asymptomatic without surgery, 21% of asymptomatic patients eventually had symptoms, and two of these had electrosurgery. SCD, sudden cardiac death; OR, subsequent surgery because of symptom development; Sxs, symptomatic at follow-up; Asxs, asymptomatic at follow-up.

FIGURE 5. Bar graph showing relation between age at diagnosis and subsequent symptom status among 53 residents of Olmsted County, Minnesota, with asymptomatic Wolff-Parkinson-White syndrome at initial clinical diagnosis, 1953–1989. The number of patients in each age group who had symptoms is shown in black. □, Remained asymptomatic; ■, became symptomatic.

FIGURE 6. Graph showing progression to development of symptoms among 53 residents of Olmsted County, Minnesota, with asymptomatic Wolff-Parkinson-White syndrome at initial clinical diagnosis, 1953–1989. Symptoms had developed in 30% of patients by the end of 10 years of follow-up.
The two SCDs occurred in males, both of whom had had previous documented tachycardias. The first patient (patient 2, Table 2) had significant symptoms during infancy and subsequently was asymptomatic until young adulthood; at the age of 23 years, he experienced SCD during athletic competition. Autopsy disclosed a heart weight of 520 g and left ventricular wall thickness of 18 mm (the patient was a large athlete); the coronary arteries, lungs, and brain were normal. No anatomic or toxicologic cause of death was found. The second patient (patient 6, Table 2) experienced recurrent symptoms for 3 years before his sudden death at age 32; autopsy permission was denied by the family. The incidences of SCD per patient-year for symptomatic patients, asymptomatic patients, and the overall group, respectively, were 0.0025 (95% CI, 0.0003–0.0009), 0.0000 (95% CI, 0.0000–0.0005), and 0.0015 (95% CI, 0.0002–0.0005).

**Treatment**

Thirty-two patients (28%) were under medical treatment at last follow-up. β-Blockers accounted for 58% of all patient prescriptions, and digitalis, class I antiarrhythmics, and calcium channel blockers accounted for 21%, 12%, and 9%, respectively. Nine of 113 patients (8%) had surgery. The average age at the time of surgery was 15±10 years (range, 5–45 years). Accessory pathway locations documented at the time of surgery included LFW in five patients, PS in three, and multiple (LFW and PS) in one. WPW surgery with loss of preexcitation was clearly associated with symptomatic patients becoming asymptomatic (nine of nine). Of the 43 initially symptomatic nonsurgical patients who are alive, 15 are currently asymptomatic, and only two of these 15 are taking antiarrhythmic drugs. Drug therapy was not associated with asymptomatic status at follow-up.

**Discussion**

This study allowed long-term examination of a nonselected, nonreferred local population of patients with clinically recognized WPW syndrome. It was confirmed that the incidence of SCD in such a group is low, that symptoms develop in about 30% of initially asymptomatic patients, that symptom development is associated with age <40 years at diagnosis and family history of symptoms, that WPW is intermittent in a significant minority of patients, and that the incidence of newly diagnosed cases within a population was four per 100,000 persons per year.

**Incidence and Demographic Features**

The overall incidence rate for new cases of WPW in Olmsted County, Minnesota, from 1953 to 1989 was 3.96 per 100,000 persons per year. As in previous studies, the incidence in males was more than twice that in females. The highest incidence in both sexes was during the first year of life, with secondary peaks in young adulthood. This bimodal distribution is of interest. It has been documented in previous pediatric series that many infants who were symptomatic during the first year of life became asymptomatic as they got older. This may be related in part to extensive postnatal development changes that occur in the neonatal conduction system. James documented marked degeneration and cellular resorption in areas immediately adjacent to the atrioventricular node and His bundle in postnatal preparations; it is unclear whether such postnatal changes also occur in accessory bypass tracts.

**Sudden Death**

Previous natural history studies have reported SCD rates of 0–0.6% per year in patients with WPW syndrome (Table 3). Our study was unique in many respects with reference to reporting SCD incidence in a community-based WPW population (Table 3). Both
symptomatic and asymptomatic patients were included. All age groups were included, as were women, and all patients were collected from a local, nonreferred population. In contrast, the US Air Force studies\textsuperscript{17,18} contained a paucity of women, and many subjects had been screened for flight training. Children, particularly infants, were not included in the two largest studies,\textsuperscript{16,17} and follow-up periods were shorter. All studies were organized as case series (except for a portion of one US Air Force study that contained a group of schoolchildren who were representative of a general population).\textsuperscript{18,30}

Nonetheless, the magnitude of SCD incidence disclosed in our population-based study (0.15% per year) was similar to values ascertained in previous reports (Table 3). The group of patients asymptomatic at diagnosis did extremely well, experiencing no SCD. This is entirely consistent with the study of Leitch et al,\textsuperscript{15} who reported no SCD in a group of 75 initially asymptomatic patients followed up for a mean of 4.3 years.

Symptom Development

One third of asymptomatic patients <40 years old (at diagnosis) eventually had symptoms, whereas no asymptomatic patients >40 years old (at diagnosis) had symptoms. Asymptomatic patients <40 years old and those with a family history of symptoms should be advised to return for follow-up if symptoms develop after WPW has been diagnosed.

### Episodic Preexcitation

The episodic nature of WPW, as assessed by the presence or absence of preexcitation on the surface ECG, was demonstrated. In this study, 22% of patients had an initial negative ECG. Krahm and coworkers,\textsuperscript{31} among others, noted this previously. There was no correlation of this feature to accessory pathway location (e.g., LFW), sex, age, or initial clinical features. One potential explanation for episodic preexcitation is varying autonomic tone, but there is no direct evidence for this. Another possible explanation is that the accessory bypass tracts in these 25 patients had longer effective refractory periods and, thus, were more likely to block intermittently.

### Associated Heart Disease

Previous studies have drawn an association between congenital heart lesions or dilated cardiomyopathy and the WPW syndrome.\textsuperscript{25,28,32-42} In this study, these particular cardiac diseases were present in 7% of patients. Of interest, clinically recognized Ebstein’s anomaly was conspicuously absent in our study. Because not all patients underwent cardiac ultrasonography, non-clinically recognized Ebstein’s anomaly could have gone undetected. Nonetheless, among patients who underwent WPW surgery at our institution, approximately 10% had coincident Ebstein’s anomaly, suggesting that the combination in a community-based population is relatively uncommon.
Study Limitations

Underestimation of the true incidence of WPW and the associated SCD rate by this study may have occurred for several hypothetical reasons. First, not every resident of Olmsted County had an ECG recorded during the study period. However, preexcitation can be intermittent and episodic; therefore, it is likely that some individuals with bypass tracts would not have been identified even if all residents had had an ECG recorded. In our series, 22% of the cohort had no preexcitation evident on the first recorded ECG. This group included asymptomatic patients as well as patients who later had symptoms and eventually required surgery.

A second consideration is the possibility that WPW patients may have experienced SCD before any ECG. In a series of young patients resuscitated from SCD who later underwent electrophysiological study, 14% were demonstrated to have WPW.44 Olmsted County data from the last four decades suggest that approximately 35 young people (1–40 years old) have died suddenly (not of trauma or drug overdose)45–46; in conjunction with the report of Topaz et al.,44 these data suggest that, potentially, another three or four SCDs attributable to WPW may have been missed. Additionally, it is possible that the natural history of symptomatic patients was favorably altered through surgical or pharmacological treatment (or both), thus also minimizing the incidence of SCDs in this cohort. However, any additional hypothetical SCDs might have been balanced by detection of additional WPW cases using complete repetitive population screening.

Finally, the most recent available census data for Olmsted County, Minnesota, revealed the ethnic distribution to be 95.7% Euro-American, 3.0% Asian American, 0.7% African American, 0.3% Native American, and 0.3% other. Thus, the data within this study came from a homogeneous ethnic group of patients and may not be readily applicable to large multiethnic urban areas.

Despite these conjectured limitations, the present population-based study provides the most comprehensive estimate available of the incidence of WPW syndrome and its natural history in a community setting.

Conclusions

In summary, at least ≈50% of the members of community WPW cohort were asymptomatic at diagnosis. The highest incidence of new cases was seen in infancy, and 23% of the patients were diagnosed during the pediatric years. No SCD occurred in the initially asymptomatic group of patients over an extended period of follow-up; this supports the suggestion of Klein et al.13 that electrophysiological study not be performed routinely in this group of patients. However, clinical follow-up of young asymptomatic individuals is necessary because 30% proceed to have symptoms, even after 10 years of asymptomatic follow-up. Symptomatic infants who become asymptomatic after the first year of life should continue to have regular monitoring well into young adulthood, since some can regain symptoms and experience SCD (see patient 2, Table 2). In adults, after the fourth decade of life, symptoms can occur,47 but they do so much less frequently.

It appears that an initial, single ECG missed WPW syndrome in nearly 25% of the Olmsted County cohort. Thus, any effort to establish an absolute WPW incidence by mass population screening using a single ECG recording will be thwarted and will provide at most a lower limit for the actual value. Nevertheless, the group of relatively undetected patients with intermittent preexcitation have a minimal chance of suffering SCD, because they cannot sustain a rapid ventricular response during atrial fibrillation.43

References


47. Rosenfeld LE, Zetta AM, Batsford WP: Comparison of clinical and electrophysiological features of preexcitation syndromes in patients presenting initially after age 50 years with those presenting at younger ages. Am J Cardiol 1991;67:709-712
T M Munger, D L Packer, S C Hammill, B J Feldman, K R Bailey, D J Ballard, D R Holmes, Jr and B J Gersh