Familial Pseudo-Wolff-Parkinson-White Syndrome

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Familial pseudo-WPW syndrome. ***Introduction:*** **PRKAG2 plays a role in regulating metabolic pathways, and mutations in this gene are associated with familial ventricular preexcitation, hypertrophic cardiomyopathy, and atrioventricular conduction disturbances. Clinico-pathologic and experimental data suggest the hypothesis of a glycogen storage disease.**

Objective: **To report a unique pattern of clinical features observed in individuals with a mutant PRKAG2 from two unrelated families.**

Methods and Results: **We studied two large families and found a total of 20 affected individuals showing a combination of sinus bradycardia, short PR interval, RBBB, intra and infrahisian conduction disturbances often requiring a pacemaker, and atrial tachyarrhythmias. Three individuals died suddenly at a young age. No patient had the Wolff-Parkinson-White (WPW) syndrome, and only two patients (10%) had myocardial hypertrophy. We performed screening of the exons and exon-intron boundaries of PRKAG2. Genetic analysis revealed a missense mutation (Arg302Gln) in the affected individuals from both families. This mutation had been described before and has been associated with the familial form of the WPW syndrome and with a high prevalence of left ventricular hypertrophy.**

Conclusion: **PRKAG2 mutations are responsible for a diverse phenotype and not only the familial form of the WPW syndrome. Familial occurrence of right bundle branch block, sinus bradycardia, and short PR interval should raise suspicion of a mutant PRKAG2 gene.** *(J Cardiovasc Electrophysiol, Vol. 17, pp. 724-732, July 2006)*

prkag2, missense mutation, familial RBBB and short PR interval, familial atrioventricular block, familial atrial flutter, familial atrial fibrillation, sinus bradycardia, sick sinus syndrome

Introduction

The association between Wolff-Parkinson-White (WPW) syndrome, left ventricular (LV) hypertrophy, and atrioventricular (AV) conduction disturbances was recognized in the 1980s,[1] and it has not been until these last years that mutations in PRKAG2, encoding for the γ_2-subunit of the adenosine monophosphate-activated protein kinase, have been identified as responsible for this complex phenotype.[2-4] This disease is associated with severe rhythm conduction disturbances, often requiring implantation of a pacemaker, atrial fibrillation, and myocardial hypertrophy. Clinico-pathologic[5] and experimental data[6,7] suggest that myocardial hypertrophy associated with PRKAG2 mutations is a glycogen storage cardiomyopathy. Transgenic mice overexpressing the PRKAG2 cDNA and showing elevated AMP-activated kinase activity accumulated large amounts of cardiac glycogen and developed dramatic LV hypertrophy, postnatal ventricular preexcitation, and sinus node dysfunction. In this complex phenotype, variable expressivity has been observed. In all families, ventricular preexcitation is the most prevalent finding, and hypertrophy appears to be present in some but not all individuals with the PRKAG2 mutations.[8] The clinical features that suggest the presence of a PRKAG2 mutation include familial occurrence of ventricular preexcitation, myocardial hypertrophy resembling hypertrophic cardiomyopathy, early onset of AV conduction disturbances, and atrial tachyarrhythmia.[3,8] We report a unique pattern of clinical and electrocardiographic abnormalities caused by a previously identified missense mutation (Arg302Gln) in 20 members of 2 unrelated families showing a peculiar electrocardiogram (ECG) consisting of sinus bradycardia, RBBB with a short PR interval, high incidence of counterclockwise atrial flutter and atrial fibrillation, sinus bradycardia, and conduction system disturbances, with an ECG suggestive of ventricular preexcitation but without the WPW syndrome.

Methods

Study Population

Informed and written consent was obtained from study subjects. Upon the suspicion of an inherited genetic disorder, we investigated 80 members from three generations of the *Bonfim* family, and 27 members of three generations of the *Luz* family. Each individual underwent a 12-lead ECG, a chest X-ray, transthoracic echocardiogram, and blood drawing for genetic analysis. Affected individuals underwent a follow-up ECG and echocardiogram in May 2005.

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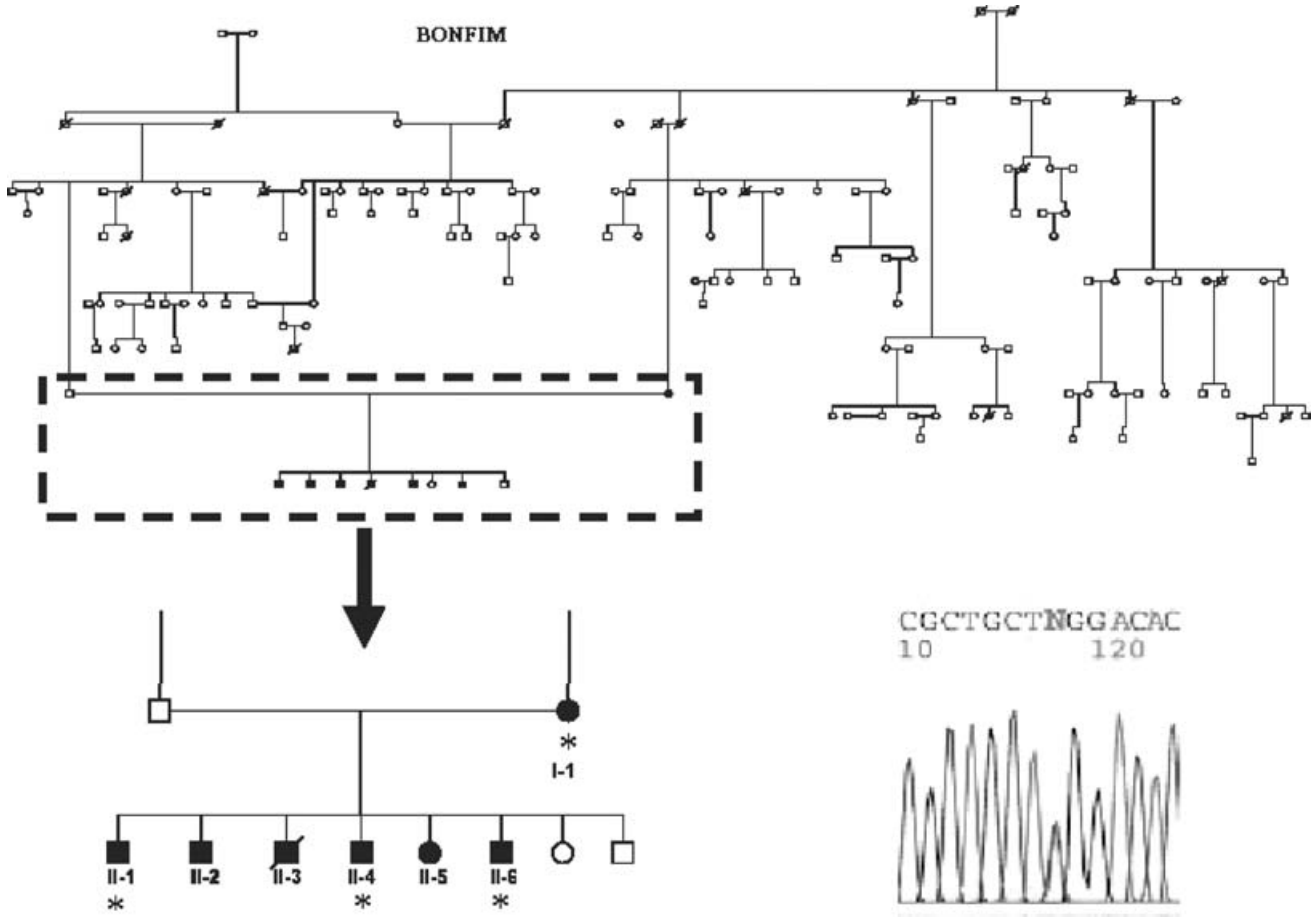

Figure 1. *Pedigree of the Bonfim family. Solid symbols denote affected members (circles are female family members and squares are male family members), and symbols with a slash denote deceased family members. The member who died suddenly from a likely cardiac cause is depicted as a solid slashed square. Asterisk indicates individuals with a pacemaker.*

Bonfim family

Six siblings (five male) among eight had a similar ECG pattern of a right bundle branch block with a short PR interval, without ST-T segment abnormalities. The father, aged 65 years, and the two other siblings, one male aged 42 years, and one female aged 38 years, were asymptomatic and had a normal ECG. We found that in this family, intermarriage between cousins was a common event for many generations (see Fig. 1). *Bonfim* family members are Caucasians.

All members live in the town of Bonfim, state of Minas Gerais, Brazil. Bonfim is not considered an endemic region of Chagas' disease (the triatomine bug responsible for the transmission of the *Trypanosome cruzi* [*T. cruzi*] to humans has not been found in that particular region). Notwithstanding, since Chagas' heart disease is one of the leading causes of right bundle branch block in young people in Minas Gerais, we carried out blood tests for *T. cruzi* infection with hemagglutination[9] and ELISA indirect immunofluorescence.[10]

Luz family

All family members are mulattos (Fig. 2). They live in the south of Bahia state (1,300 km from the town of Bonfim). The patients were followed at the University Hospital of Federal University of Bahia during the last 9 years. All patients were tested for Chagas' disease.

Electrophysiologic Assessment

Programmed electrical stimulation and recordings of the 12-lead surface ECG and intracardiac electrograms were made using the EP Tracer or MS System (CardioTek BV, Maastricht, The Netherlands).

Genetic Analysis

The study was approved by the Regional Institutional Review Board, and the individuals gave written consent to participate in the study. Blood samples (10 mL) were obtained from participating family members and spouses. Genomic DNA was isolated from peripheral blood leukocytes using a commercial kit (Gentra System, Puregene, Minneapolis, MN, USA). Exons and intron-exon boundaries of PRKAG2 were analyzed using direct sequencing. Polymerase chain reaction products were purified with a commercial reagent (ExoSAP-IT, USB Corporation, Cleveland, OH, USA) and were directly sequenced from both directions with the use of ABI PRISM 3100 Automatic DNA Sequencer.

Statistical Analysis

Values are given as mean ± standard deviation. The significance of differences ($P < 0.05$) between groups of clinical, electrocardiographic, or electrophysiologic (EP) parameters was assessed by Student's *t*-test or Fisher's exact test.

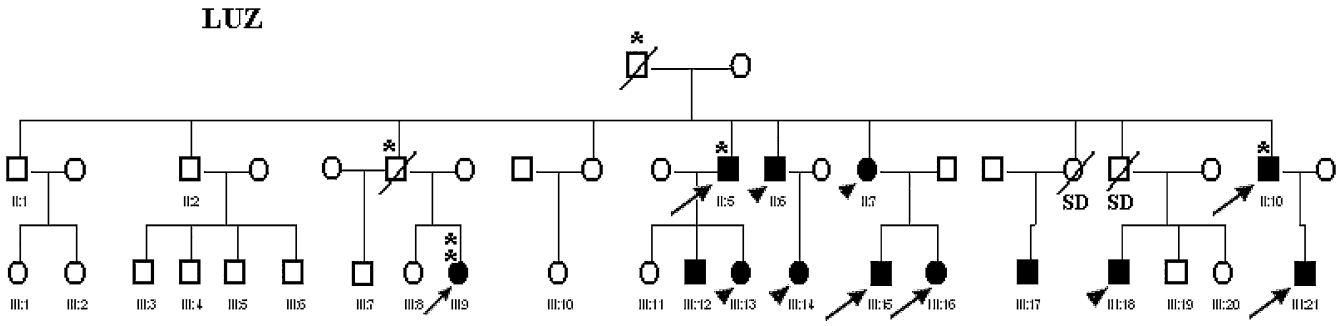

Figure 2. *Pedigree of the Luz family. Asterisk indicates individuals with a pacemaker. A double asterisk indicates the patient with an ICD. A solid symbol indicates a carrier of PRKAG2 mutation. A black arrow points to individuals with an ECG pattern of RBBB and short PR interval, and the black arrowhead points to individuals with a short PR interval without RBBB. SD means sudden death. Individuals who had blood samples collected for genetic analysis are shown with an identification number bellow the symbol.*

Results

Clinical Evaluation

Blood tests for Chagas' disease yielded negative results in all individuals tested from both families. The onset of clinical symptoms typically occurred from the second through the third decade.

Bonfim family

The affected members of the *Bonfim* family were regularly seen in the outpatient clinic and have a mean follow-up of 85 ± 47 months. Apart from Case II-1, who developed LV hypertrophy during long-term follow-up, no other individual, including case 3 who died suddenly, had any structural abnormalities in the heart. The affected individuals of the *Bonfim* family comprised seven individuals (five males), with a mean age of 40 ± 14 (ranged from 20 to 55) years.

Clinical presentation

Atrial arrhythmia: An atrial tachyarrhythmia was the first manifestation of the disease in four male siblings. Case II-1 had recurrent counterclockwise atrial flutter in addition to a mild hypertension since the age of 20 years. A DDD pacemaker was implanted 4 years later due to intermittent third-degree AV block. At the age of 31 years, he was admitted for cavo-tricuspid isthmus catheter ablation because of a pacemaker-mediated tachycardia due to tracking of atrial flutter. He developed persistent atrial fibrillation at the age of 34 years. Case II-2 (26-year-old male) came to medical attention because of palpitations and fatigue caused by an incessant counterclockwise atrial flutter with a heart rate of 150 bpm. Case II-5 had paroxysmal short-lived bouts of atrial flutter. These siblings also underwent cavo-tricuspid isthmus catheter ablation, and no recurrence of atrial flutter occurred thereafter. Cases II-3 and II-4 presented with atrial fibrillation and a fast heart rate (200–280 bpm). Case I-1 had chronic atrial fibrillation for 2 years before a third-degree AV block was diagnosed during an emergency admission because of Adams-Stokes episodes. In summary, an atrial tachyarrhythmia, either symptomatic or silent, was the first clinical event in five of the seven affected individuals in the *Bonfim* family.
Syncope and advanced AV block: Case I-1 developed advanced heart block at the age of 54 years, case II-1 developed syncope 4 years after the onset of the atrial flutter, and case II-4 developed syncope at the age of 32 years.

Sudden death

Case II-3 spontaneously discontinued oral amiodarone more than 6 months before dying suddenly. He had fast irregular palpitations followed by syncope. He recovered consciousness and, according to one eyewitness, he collapsed again and died suddenly on the way to the nearest hospital. At admission, a 12-lead ECG recorded ventricular fibrillation. He was 32 years old. An autopsy was not performed.

Electrocardiogram

Five of the seven affected individuals had sinus bradycardia, short PR interval, RBBB with normal QRS frontal plane axis (Fig. 3). The ECG pattern in most patients is suggestive of ventricular preexcitation (Figs. 3 and 4), due to an association of a short PR interval with an enlarged and slurred QRS complex, mimicking a delta wave. Case I-1 had atrial fibrillation with RBBB documented 2 years before she developed advanced heart block Case II-4 had normal sinus rhythm, short PR interval, and a narrow QRS complex at presentation (23 years old). Four years later the 12-lead ECG showed a RBBB pattern.

Transthoracic echocardiogram

The first echocardiogram showed no abnormalities in any of the seven affected individuals. Only case II-1 developed a nonobstructive asymmetric LV hypertrophy (posterior wall of 1.3 cm and septum of 2.1 cm), which was not detected at presentation (12 years before).

Electrophysiologic study

Six siblings underwent an EP study (Table 1). Programmed ventricular stimulation yielded no sustained ventricular tachycardia. All patients showed an AH interval of less than 60 msec. Assessment of atrioventricular conduction showed prolongation of intraatrial conduction time in one patient (II-6), second-degree intrahisian block in one patient (II-6) (Fig. 5), and pacing-induced second-degree infrahisian block in one patient (II-4). Case I-1 underwent an EP study because of an atrial flutter with pacemaker-mediated tachycardia. Case II-2 underwent two EP studies. Radiofrequency

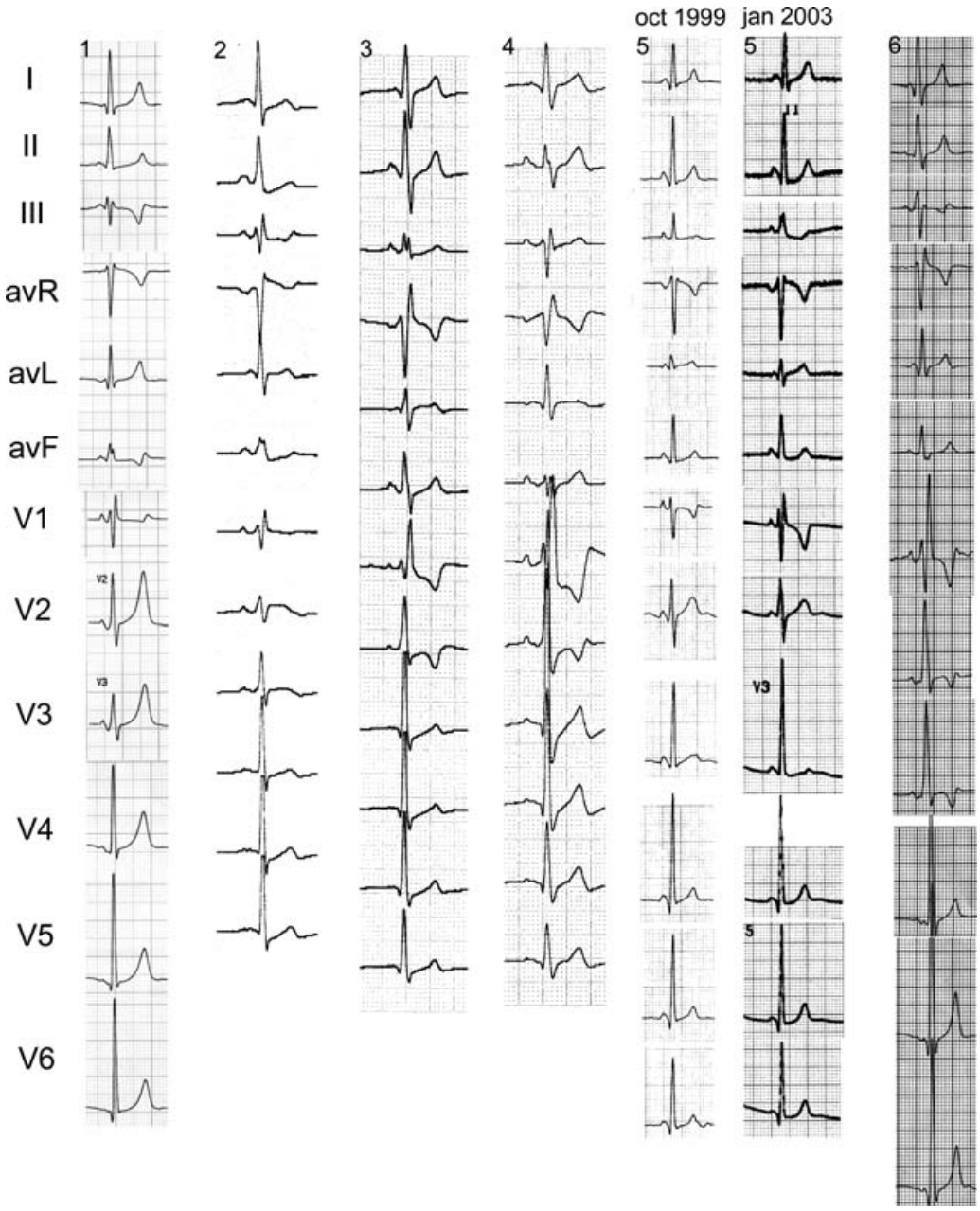

Figure 3. *Twelve-lead ECG of the affected siblings from the Bonfim family (before pacemaker implantation in cases 1, 4, and 6). The first ECG of case 5 shows a short PR interval recorded in 1999 and the second in 2003 shows a right bundle branch block pattern in addition to the short PR interval.*

catheter ablation of a counterclockwise atrial flutter was performed during the first procedure. A second procedure was performed 6 years later to assess AV conduction. There was no evidence of infranodal conduction disturbance, and in spite of sinus bradycardia, sinus node recovery time and sino-atrial conduction time were within the normal range. Assessment of the AV nodal conduction by atrial pacing at increasing rates showed a decremental response, but with a maximal delta-AH interval of 90 msec (some intraatrial conduction delay is probably also included in this measurement) (case II-6) (Fig. 6). The mean maximal prolongation of the AH interval was 52 ± 20 msec.

Three patients were challenged with a bolus ranging from 6 to 9 mg of intravenous adenosine: cases II-2, II-5, and II-6. There was a slight and transient prolongation of the AH interval in cases II-2 and II-6 (40 and 60 msec, respectively), and case II-6 responded with AV nodal 2:1 conduction block.

Luz family

Six individuals from three generations showed the ECG pattern of short PR interval, sinus bradicardia, and RBBB (Fig. 4), while five individuals had sinus bradycardia and short PR interval. Two patients required implantation of a pacemaker (symptomatic sinus bradycardia in one patient and complete AV block in the other). One young woman (individual III-8) (Fig. 2) required implantation of an ICD (primary prevention) due to recurrent syncope. She was the only proband of the *Luz* family having LV hypertrophy (echocardiogram showed asymmetric hypertrophy with a 22-mm

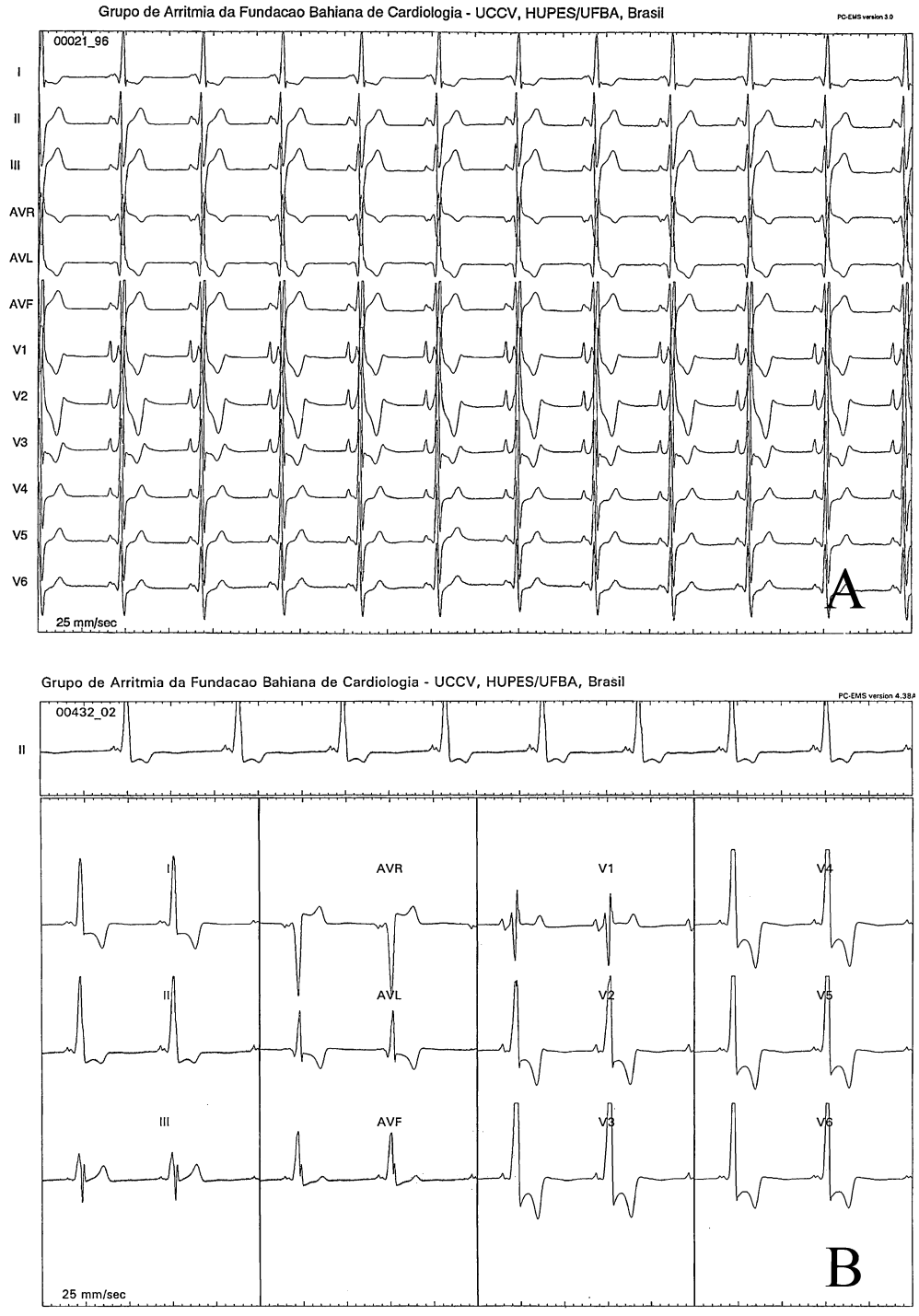

Figure 4. *Luz family: Panel A (Individual II-8) and panel B (individual III-16). The 12-lead ECG shows the same pattern of sinus bradycardia plus RBBB and short PR interval, as in the affected members of the Bonfim family.*

interventricular septum and LV posterior wall thickness of 10 mm). Two patients (individuals II-8 and II-9) had sudden unexpected death at the age of 38 and 40 years, respectively. Electrophysiology assessment was carried out in only two probands of the *Luz* family (individuals II-10 and III-8) (Table 1). No sustained ventricular tachycardia was induced, even in the patient with LV hypertrophy. No autopsy was performed.

One patient had atrial flutter and three patients had atrial fibrillation.

Genetic Analysis

Direct sequencing of the PRKAG2 gene revealed a missense mutation in exon 7—Arg302Gln. The same mutation was found in six individuals from the *Bonfim* family (five siblings showing the right bundle branch with short PR interval and in their mother) and in 13 individuals from the *Luz* family. This mutation has been previously described in the familial form of the WPW, and it is the most common mutation in the WPW and LV hypertrophy phenotype. It has

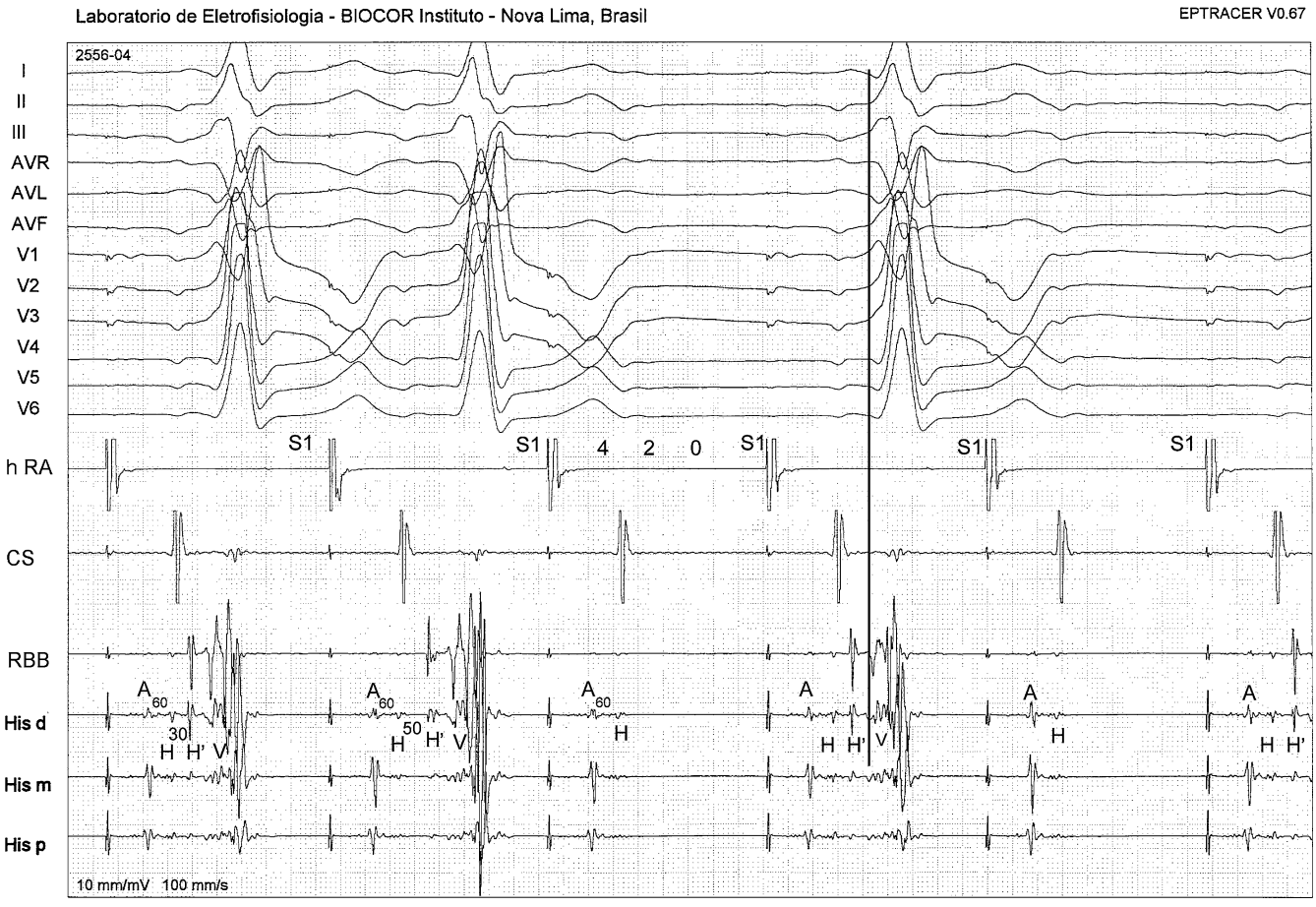

Figure 5. *(Case 6, Bonfim family) Intrahisian Wenckebach block during atrial pacing (cycle length of 420 msec). Note the large spike-A interval consistent with intraatrial conduction disturbance. A black line was draw to mark the onset of the QRS complex (HV interval = 35 msec).*

been identified in seven families,[11] and a transgenic mouse model has already been developed with the characteristic phenotype.

Summary of the Main Findings in Both Families

Twenty individuals were carriers of the missense mutation (Arg302gln). There were 14 males (70%). The mean age was 31 ± 12 years, 18 of 20 (90%) had sinus bradycardia, 13 of 20 (65%) had RBBB plus short PR interval, 5 of 20 (25%) had short PR interval, 2 of 20 (10%) developed nonobstructive asymmetric LV hypertrophy, 8 of 20 received a pacemaker, and no patient had the WPW syndrome. His bundle pacing was performed in order to rule out the presence of an atrioventricular bypass tract. It was carried out in five of eight patients, and there was no change in the QRS complex as seen during sinus rhythm. A diagnosis of a fasciculoventricular pathway was ruled out because the HV interval was >35 msec in all eight patients who underwent electrophysiologic study.

Discussion

Previous studies[2–5] have reported mutations in the gene PRKAG2 (Arg302Gln) of the chromosome 7 in patients with the familial form of the WPW syndrome. In these families there was a high incidence of associated LV hypertrophy. A slightly different missense mutation of PRKAG2 (Arg531Gln) was associated with familial WPW in the absence of LV hypertrophy.[8] PRKAG2 mutation was not found in a cohort of 109 patients with nonfamilial WPW syndrome.[12] In contrast, a mutant PRKAG2 (a single base change at the exon 9) was found in four children with sporadic WPW syndrome associated with LV hypertrophy.[13] We describe a new phenotype caused by a mutant PRKAG2 gene in 20 individuals from two unrelated families in the absence of the WPW syndrome. It is worth noting that the incidence of LV hypertrophy in the affected patients was only 10% (only 2/20 patients) as compared with the incidence of 75% in the familial WPW syndrome.[5] The AV conduction disturbances in our patients were multilevel. We found prolongation of intraatrial, intrahisian, infrahisian, and intraventricular conduction times. The distinctive ECG pattern found in 12 of our 20 (60%) patients—sinus bradycardia, RBBB with a short PR interval—was caused by a striking association of a conduction block in one structure (the right bundle branch) with fast conduction in another (the AV node). It is worth noting that six affected individuals showed sinus bradycardia with a short PR, and one of them developed RBBB during the follow-up (*Bonfim* family case II-5). A longer follow-up will be needed to assess the role of the short PR interval as a marker of severe AV conduction disturbances in carriers of a mutant PRKAG2. No patient presented with a LBBB. The high incidence of RBBB pattern might be explained due to

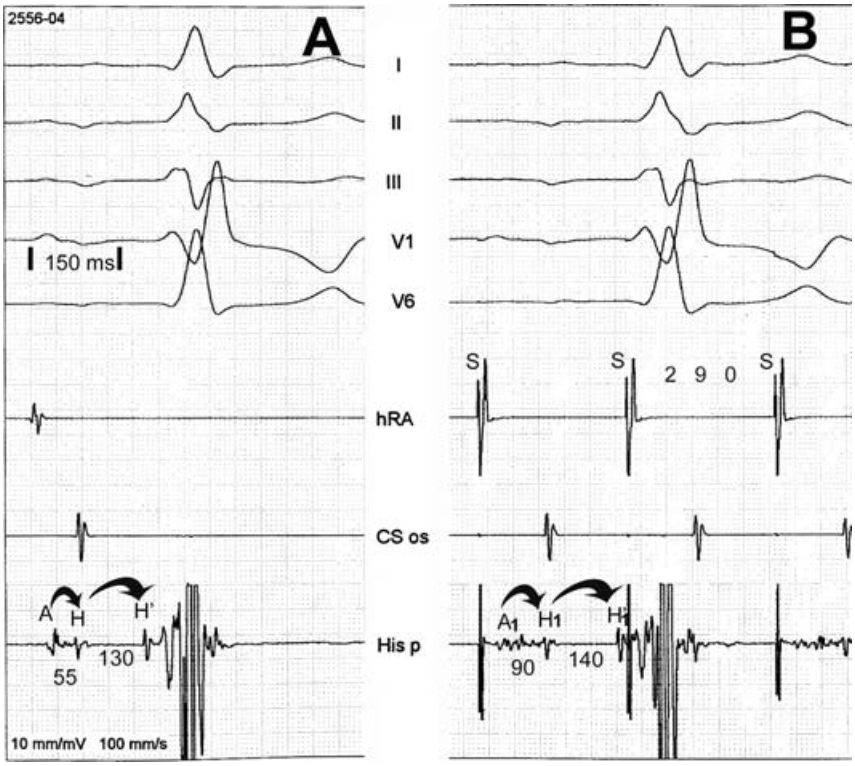

Figure 6. *(Case 6, Bonfim family) Assessment of AV nodal conduction during sinus rhythm (panel A) and rapid atrial pacing (panel B). The first and the second arrows represent AH and HH' conduction, respectively. Conduction through the AV node is still unblocked at 290 msec. However, there is a 2:1 intrahisian block. AH interval increased from 55 to a maximum of 90 msec before AV nodal block occurred (not shown). The time interval of 150 msec between the two solid bars at the top of panel A is indicative of prolonged conduction time between the right and the left atrium.*

anatomical reasons. A much higher incidence of RBBB over LBBB is also observed in Chagas' heart disease (usually associated with left axis deviation).

The mean maximal prolongation of the AH interval during atrial pacing at increasing rates was 52 ± 20 msec, but other EP criteria for a complete bypass of the AV node (atriohisian bypass tract) as a short HV interval or the absence of a His bundle potential were lacking. Our observations of a short baseline AH interval and a blunted response to atrial pacing (with an increase of less than 100 msec) (Table 1) are consistent with a "small" AV node in most patients. However, two of the three patients from the *Bonfim* family who had 1:1 AV conduction with atrial pacing at rates beyond 200 bpm had spontaneous bouts of atrial fibrillation with very fast ventricular rates, suggesting the presence of an "enhanced" AV node conduction.[14] AV conduction disturbances occurred early in life and very often caused life-threatening symptoms requiring pacemaker implantation. The mechanism of death in *Bonfim* family case 3 remains speculative, but ventricular fibrillation was probably precipitated by atrial fibrillation with a fast ventricular rate.

Phenotype Similarities with Previously Described Families with PRKAG2 Mutations

Previous studies reported an incidence of atrial tachyarrhythmia ranging from 38% to 44% of the patients. Five of the seven affected patients from the *Bonfim* family had atrial fibrillation and/or atrial flutter (71%) (P = ns). Incidence of atrial tachyarrhythmias was much lower in the *Luz* family (30%). That difference could be explained by the lower age of the carriers in the *Luz* family (27 ± 13 years) as compared with the *Bonfim* family (40 ± 14 years) (P = 0.04). It is possible that the incidence of atrial tachyarrhythmias will increase over time. Progression of a high-degree sinoatrial or atrioventricular block requiring the implantation of a pacemaker occurred in 76% of the affected individuals who were older than 30 years of age in the study of Gollob et al[3] In our cohort of 20 patients, 6 required implantation of a pacemaker (30%) (P = ns).

Phenotype Dissimilarities with Previously Described Patients with PRKAG2 Mutations

Not a single individual in our cohort showed ventricular preexcitation, contrasting with previous clinical and experimental studies reporting PRKAG2 mutations showing a very high incidence of preexcitation. However, we believe that the 12-lead ECG is highly suggestive of the presence of ventricular preexcitation (Figs. 3 and 4). It has been suggested[13,15] that ventricular preexcitation associated with a mutant PRKAG2 involves either a decrementally conducting accessory pathway or a fasciculoventricular pathway in many instances. A fasciculoventricular pathway can be difficult to recognize due to the minimal preexcitation pattern and the rather narrow QRS complex.[16–19] However, in the eight patients from our cohort who underwent an EP assessment, we found a normal HV interval, ruling out the presence of such variants of preexcitation. In addition, His bundle pacing, which was carried out in five of eight patients, yielded no change in the QRS complex morphology.

Cardiac hypertrophy was also a central and important finding in those patients with the familial form of the WPW syndrome. Gollob et al.[3] reported 26% incidence (8/31 patients evaluated), but hypertrophy was not present in a substantial subset of younger subjects. Three of those eight patients evolved to severe ventricular dysfunction, and one patient required transplantation at the age of 42 years. Only 2 of our 20 affected patients (10%) had LV hypertrophy.

TABLE 1

Electrocardiographic and Electrophysiologic Data

	Electrocardiogram				Electrophysiologic Parameters						
	PRi	**QRS**	**QT**	**HR**	**PA**	**AH**	**HV**	**W/2:1**	**C. length**	**Delta-AH**	**Tachyarrhythmia**
1	0.12	0.16	0.44	60	35	40	35	W	360	40	A.flutter/AF
2	0.11	0.12	0.42	60	30	50	50	W	320	50	A.flutter
3	0.11	0.16	0.40	55	25	35	35	2:01	300	30	AF
4	0.12	0.16	0.42	55	30	50	50	W	280	45	AF
5	0.10	0.15	0.40	72	25	54	35	W	270	90	A.flutter
6	0.10	0.16	0.42	50	90	55	37	W	600	60	
7	0.11	0.16	0.44	60	25	35	35	W	300	85	A.flutter/AF
8	0.11	0.16	0.42	55	40	35	35	W	320	90	A.flutter/AF

1-6 = *Bonfim* family, 7-8 = *Luz* family; C = cycle; delta-AH = maximal AH interval prolongation during right atrial pacing at increasing rates up to conduction block; PR interval, QRS width, and QT interval are displayed in seconds. HR = heart rate, PA, AH, and HV intervals are displayed in milliseconds, Tachyarrhythmia = spontaneous AF = atrial fibrillation or A. flutter = atrial flutter; W/2:1 = pattern of conduction block observed during atrial pacing at increasing rates, which was either a 2:1 block (only seen in case 3) or a Wenckebach-type block.

A New Phenotype?

Other genetic determined conditions also express different phenotypes, caused by mutations in the same gene. Mutations in the sodium channel gene SCN5A (chromosome 3), can cause Brugada's syndrome, Lenegre's disease, or long QT syndrome (LQTS 3).[20]

Each element of the phenotype observed in the present series previously has been associated with PRKAG2 disease. However, the features that make these families unique are the consistency of the phenotype in early adulthood, in particular, rapid AH conduction in the absence of definitive evidence of a focal bypass tract; normal HV intervals; and, particularly, 12-lead ECG pattern showing the association of sinus bradycardia, RBBB with short PR interval without ventricular preexcitation, and late onset complete heart block.

The Importance of Recognizing Asymptomatic Affected Individuals As Well As Those Carrying a Mutant PRKAG2 Gene but without Clinical Abnormalities

In the present cohort, our finding that 30% required a pacemaker, as did 76% of the affected members in the series of Gollob et al., allowed us to perform EP evaluation in asymptomatic patients, and upon diagnosis of a severe infranodal conduction disturbance, perform primary prophylaxis of sudden death in two asymptomatic brothers of the *Bonfim* family. One might argue that a permanent pacemaker would have played a role in preventing sudden death in the two brothers of the *Luz* family who died suddenly.

A long-term follow-up is warranted in the two carriers of the *Luz* family (individuals III-12 and III-17), who had a normal ECG because, according to our observations, the disease show a clear progressive course, probably related to the intracellular glycogen accumulation.

Similar Clinical Features In Previously Reported Families

Some reports published in the 1970s describe familial occurrence of adult onset conduction disturbances, sinus bradycardia, atrial tachyarrhythmias, sudden cardiac death, myocardial hypertrophy, short PR interval, and intraventricular conduction disturbances in the absence of the WPW syndrome.[21,22] Genetic evaluation was not available at that time but the clinical picture described is consistent with our observations in the affected individuals reported in our study.

Conclusions

PRKAG2 mutations are responsible for a diverse phenotype and not only the familial form of the WPW syndrome. Familial occurrence of the ECG pattern comprising sinus bradycardia, right bundle branch block, and a short PR interval should raise suspicion of a mutant PRKAG2 gene.

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