A large family characterised by nocturnal sudden death

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Background. We recently identified a novel mutation in large family characterised by premature nocturnal sudden death. In the present paper we provide an overview of the findings in this family.
Methods. From 1958 onwards, when the first patient presented, we collected clinical data on as many family members as possible. After identification in 1998 of the underlying genetic disorder (SCN5A, 1795insD), genotyping was performed diagnostically.
Results. Since 1905 unexplained sudden death occurred in 26 family members, 17 of whom died during the night. Besides sudden death, symptomatology was rather limited; only six patients reported syncopal attacks. In one of them, a 13-year-old boy, asystolic episodes up to nine seconds were documented. Until now, the mutation has been found in 114 family members (57 males, 57 females). Carriers of the mutant gene exhibited bradycardia-dependent QT-prolongation, intrinsic sinus node dysfunction, generalised conduction abnormalities, a paucity of ventricular ectopy, and the Brugada sign. Cardiomyopathy or other structural abnormalities were not found in any of the carriers. Electrophysiological studies showed that mutant channels were characterised by markedly reduced I_{Na} amplitude, a positive shift of voltage-dependence of activation and a substantial negative shift of voltage-dependence of inactivation of I_{Na}. From 1978 onwards, a pacemaker for anti-brady pacing was implanted for prevention of sudden death. In patients in whom a prophylactic pacemaker was implanted no unexplained sudden death occurred, whereas 5 sudden deaths occurred in the group of patients who did not receive a pacemaker.
Conclusion. We have described a large family with a SCN5A-linked disorder (1795insD) with features of LQT_3, Brugada syndrome and familial conduction system disease. Anti-brady pacing was successful in preventing sudden death. The mode of death is possibly bradycardic. (Neth Heart J 2002;10:304-12.)

Key words: sudden death, long-QT syndrome, Brugada syndrome, SCN5A, pacemaker

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In patients surviving cardiac arrest an extensive diagnostic work-up is usually performed to identify the underlying disorder. In the majority of patients structural heart disease is demonstrable, but in a sizeable subset of patients no structural abnormalities can be found. The long-QT syndrome (LQTS) is an established cause of sudden death in subjects with otherwise normal hearts.[1,2] More recently, another non-structural but potentially lethal cardiac disorder was identified, the Brugada syndrome.[3,4] Genetically determined ion-channel defects have meanwhile been found to be responsible for LQTS and Brugada syndrome. In LQTS, two K^+ channels are involved,[5] but also mutations of the cardiac Na^+-channel gene (SCN5A), located on chromosome 3 (3p21). The latter form of LQTS is referred to as type 3 (LQT_3). SCN5A mutations have also been identified in patients

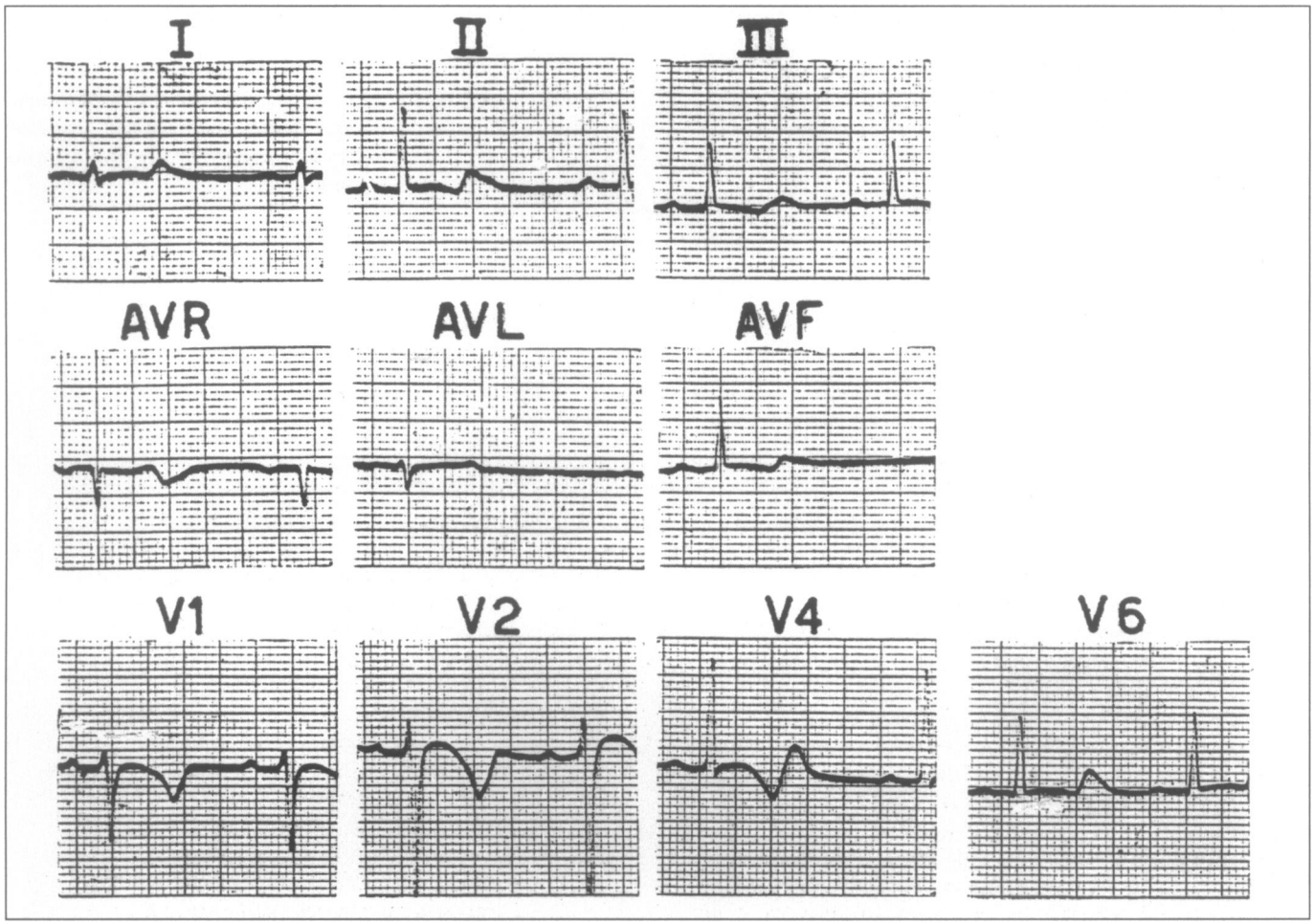

Figure 1. Original electrocardiogram of the 16-year-old boy at presentation in 1958. The QT interval and QTc are prolonged (0.60 s and 0.55 s, respectively). Other prominent features are a long isoelectric ST segment preceding a sharp T wave in lead I and V_6 and biphasic and negative T waves in leads II, V_2 and V_4.

with the Brugada syndrome.[6] Recently, we described a large family characterised by premature nocturnal sudden cardiac death and features of both LQT_3 and Brugada syndrome, often in the same individuals.[7-14] The underlying genetic disorder was found to be a mutation in SCN5A (1795insD). The present paper provides an overview of the salient findings in this remarkable family, including the historical sequalae.

Phenotype and genotype

General aspects

The family came to our attention in 1958 when a 16-year-old boy was referred to the Department of Internal Medicine, University Hospital, Groningen (Head: Professor Van Buchem) because of an abnormal electrocardiogram (ECG), taken as part of a routine sports examination. The attending physician (AAW) confirmed the presence of marked repolarisation abnormalities (figure 1). Of interest, the repolarisation abnormalities largely disappeared when the heart rate was higher. The boy did not have any symptoms and no structural cardiac disease was apparent. However, the family history was remarkable in that many family members had been the victim of unexpected nocturnal sudden death, including his mother, two sisters and a brother. Not surprisingly, at the time there were no ideas about the underlying disorder. In subsequent years clinical data were collected in as many family members as possible. In addition to the standard ECG, 24-hour ambulatory electrocardiographic (Holter) monitoring, ergometry, signal-averaged ECG and echocardiography were performed as routine investigations. Electrophysiological studies were performed in selected cases. After identification of the mutation, genotyping was performed diagnostically. In May 2002, data on phenotype and genotype were thus available on 232 family members, including 78 children: 114 carriers of the mutant gene (57 males, 57 females) and 118 non-carriers (57 males, 61 fe-

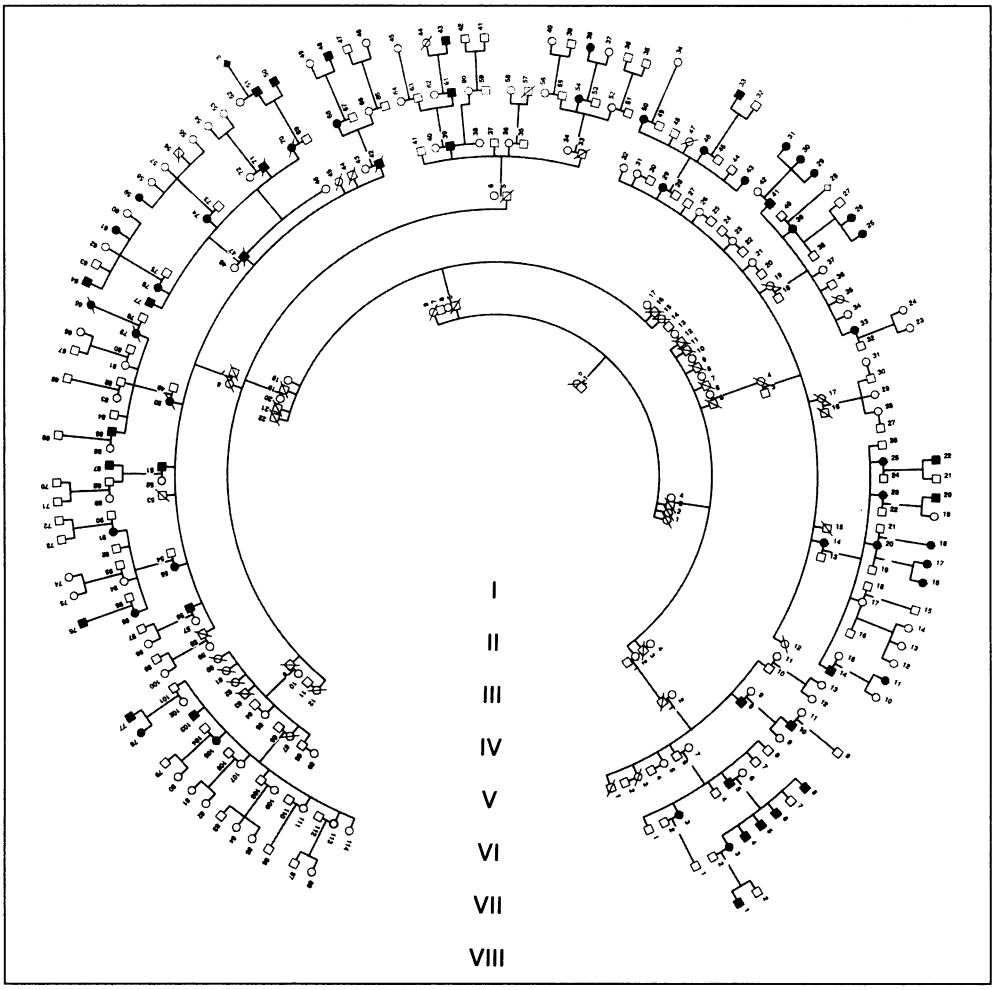

Figure 2. Part of the pedigree of the family. The pedigree has been altered to protect confidentiality. Filled circles and squares represent affected females and males, respectively. Unfilled symbols: not affected or disease status unknown.

males) (figure 2). The vast majority of family members reside in the northern part of the Netherlands.

Symptoms, sudden death

Since 1905 sudden death had occurred in 29 family members. In three of them a pacemaker was implanted for prevention of sudden death (see below). Autopsy was performed in all three subjects and revealed significant coronary artery disease, including evidence of recent myocardial infarction. Of the remaining 26 subjects with unexplained sudden death, 17 subjects died during the night, eight subjects died under unknown circumstances and one subject died in the barber's chair while being shaved. Five of the 17 nocturnal deaths were witnessed; the episodes were characterised by sudden onset of gurgling and gasping, and moaning respiration. Patients were unconscious and could not be awakened. No electrocardiographic recordings are available documenting the mode of death. Twenty of the 26 subjects with unexplained sudden death were ≤40 years (10 males, 10 females), the youngest victim being a 14-year-old girl.

Besides sudden death, symptomatology was rather limited. Only six patients reported symptoms, consisting of self-terminating syncopal attacks. In one of them, a 13-year-old boy, prolonged telemetric

Table 1. Basic demographic and ECG characteristics (only adults).

	Number	M/F (%)	Age (y)	Rate (bpm)	QTc (s)	PQ (ms)	QRS (ms)	ST-elev. (mm)
Carriers	53	47/53	38.8±14.0	65.4±16.8	0.48±0.09	0.20±0.02	115±15	1.6±1.0
Non-carriers	39	49/51	38.7±18.9	72.0±12.1	0.40±0.03	0.16±0.03	93±13	0.5±0.6
Significance, p<			NS	0.04	0.0001	0.0001	0.0001	0.0001

Bpm: beats per minute; M/F: male/female; NS: not significant; ST-elev.: ST segment elevation; y: year.

monitoring revealed asystolic episodes of up to nine seconds. In another patient, an 18-year-old male, asystole lasting 15 seconds was documented during anaesthesia. A third patient, a 61-year-old male with pre-existing first degree AV block and right ventricular conduction delay, also presented with repeated syncopal spells. His ECG showed additional left axis deviation. All three patients remained symptom-free after pacemaker implantation. Despite extensive Holter monitoring, no arrhythmias were detected in the remaining three patients with syncope. All other patients were symptom-free, although many of them were anxious.

Electrocardiogram

Findings based on 53 adult carriers of the mutant gene are given in table 1. ECGs were characterised by a relatively slow heart rate and prolongation of the PQ interval and QRS duration. However, the most striking features concerned the electrocardiographic markers of ventricular repolarisation; the QT interval corrected for heart rate was markedly prolonged in the carriers compared with the non-carriers and clearly exceeded the upper limit of normal both in males and females. Importantly, also the morphology of the STT segment was typical: most patients demonstrated a long iso-electric ST segment preceding a sharp T wave, and many patients demonstrated biphasic T waves in one or more precordial leads. Further, in a large subset of carriers (49%) the ECG was characterised by slight elevation of the ST segment in the right precordial leads ('Brugada sign'). In four carriers the effect of procainamide/flecainide and in three carriers the effect of lidocaine/mexilitine was tested: the former agents caused an increase in ST-segment elevation, whereas the latter agents caused shortening of the QT interval. Of note, the long follow-up allowed comparison of ECGs taken at distant time intervals (up to 40 years). Taken together, the ECG findings were very stable over time, including the QT interval.

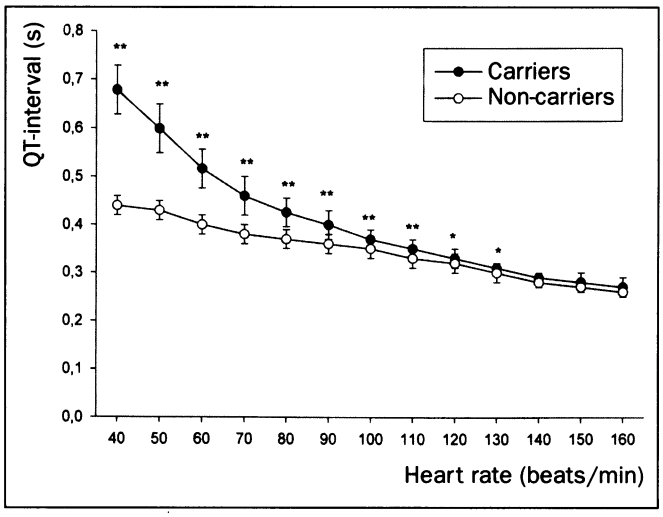

Figure 3. Relation between heart rate and QT interval for carriers and non-carriers. Values from 40 to 100 beats/min are based on Holter monitoring and values from 110 to 160 beats/min on ergometry. QT intervals are longer in carriers than in non-carriers, particularly during low heart rate, but persist up to 130 beats/min. ** p<0.001; * p<0.05. Reproduced from: Berg MP van den, Wilde AAM, Viersma JW, Brouwer J, Haaksma J, Hout AH van der, et al. Possible bradycardic mode of death and successful pacemaker treatment in a large family with features of both long QT syndrome type 3 and Brugada syndrome. J Cardiovasc Electrophysiol 2001;12: 630-6 with permission.

Holter monitoring

Holter monitoring, which first became available in Groningen in 1978, was a key tool in establishing the phenotype. Findings in 54 adult carriers are given in table 2 and figure 3. Briefly, recordings were characterised by relative bradycardia (throughout the entire day) and excessive prolongation of the QT interval at slow heart rates. As a result, QT intervals were often very long, occasionally exceeding one second (figure 4). Of note, sudden changes in heart rate had an

Table 2. Holter monitoring.

	Carriers n=54	Non-carriers n=40	P-value
Mean heart rate (bpm)	70±8	77±9	<0.001
Lowest heart rate (bpm)	41±8	47±8	<0.001
Highest heart rate (bpm)	124±24	141±16	<0.001
Longest RR interval (s)	1.74±0.45	1.57±0.44	NS
QT at lowest heart rate (s)	0.68±0.10	0.44±0.03	<0.001
QT_c at lowest heart rate (s)	0.55±0.06	0.38±0.02	<0.001
Total number of VPBs	0 (0-2149)	1 (0-2009)	0.004
Total number of APBs	1 (0-846)	2 (0-3199)	0.023

Bpm: beats per minute; NS: non-significant; APB: atrial premature beat; VPB: ventricular premature beat.
Data adapted from reference 11.

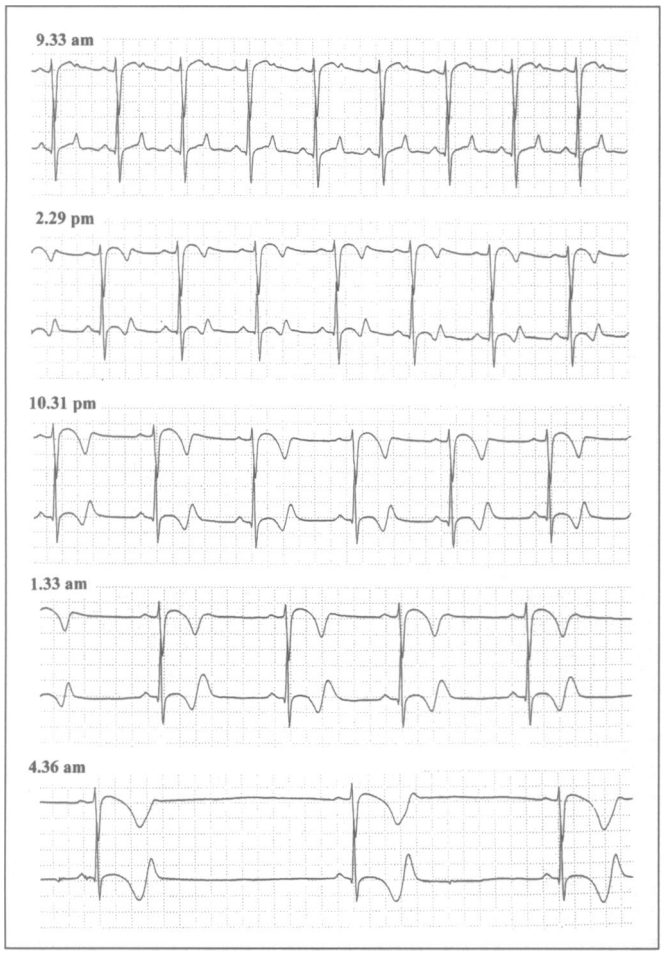

Figure 4. Representative rhythm strips obtained during Holter monitoring. During the day when heart rate is relatively high the repolarisation abnormalities are modest. However, repolarisation abnormalities are marked during the night, which is compounded by concomitant sinus bradycardia.

instantaneous effect on subsequent repolarisation; that is, any RR interval prolongation caused immediate further perturbation of the STT segment. Heart rate variability parameters were comparable among carriers and non-carriers (data not shown), indicating that bradycardia was not due to increased vagal tone. Another feature was the paucity of both atrial and ventricular premature beats. In fact, in the vast majority of carriers (71%) there were no ventricular premature beats and complex ventricular arrhythmias were not noted in any of the carriers. In three patients T-wave alternans was recorded. Prior Holter recordings available in three carriers who died suddenly were unremarkable compared with recordings from the other carriers.

Ergometry

The highest attained heart rate during symptom-limited bicycle ergometry was lower in 43 adult carriers than in non-carriers (153±18 vs 165±16 beats/min).[11] Importantly, no significant ventricular arrhythmias were noted. The effect of exercise on the QT interval is shown in figure 3. At low heart rates, the QT interval was markedly longer in the carriers, but along with higher heart rates the difference in the QT interval gradually decreased.

Signal-averaged ECG

From the early nineties onwards, a signal-averaged ECG was obtained routinely.[9] Data on 29 carriers have been reported previously:[7] in 23 of them (79%) the signal-averaged ECG showed late potentials whereas only 14% of the non-carriers had late potentials.

Echocardiography

Initially, when the diagnosis was still elusive, structural heart disease was considered a possibility, in particular (hypertrophic) cardiomyopathy. When echocardiography became available, this technique was used on a routine basis. Cardiomyopathy or other structural abnormalities were not found in any of the carriers.

Clinical electrophysiology

Electrophysiological studies were performed in three patients: a 53-year-old female, a 31-year-old female and a 13-year-old boy. Results have been detailed previously.[11] Briefly, intrinsic Wenckebach cycle length and sinus node function were within normal limits in all three patients. The AH interval was normal, but the HV interval was prolonged (95, 125 and 145 ms, respectively). In the 13-year-old boy we also measured the PA interval, which also turned out to be prolonged (50 ms). Measurements of the effective refractory periods at different cycle lengths were within normal limits in all three patients. Burst-pacing and short-long-short pacing did not provoke tachyarrhythmias, either before or after adrenaline. The HV interval was measured in five more patients during pacemaker implantation and was found to be prolonged in all five (70-80 ms). Two of them were hospitalised for seven days for additional investigations, including continuous Holter monitoring. They were repeatedly aroused during sleep using a load noise, but no arrhythmias could be provoked.

Molecular biology

The mode of inheritance with equal sex distribution was compatible with an autosomal dominant disorder. In 1998 genetic studies were performed in Amsterdam to identify the underlying genetic disorder (AAMW, CRB, IMvL).

Linkage analysis in a subset of the family revealed linkage to SCN5A, whereas no linkage was detected to other long-QT syndrome loci.[7] Subsequent single-strand conformation polymorphism (SSCP) analysis of the coding region of SCN5A identified an aberrant conformer in exon 28 in clinically affected family members. DNA sequencing of exon 28 revealed

heterozygosity for a TGA insertion at position 5537. This insertion results in the insertion of aspartic acid after tyrosine 1795 (1795insD) within the highly negatively charged region of the C-terminal domain of the protein (figure 5).

Experimental electrophysiology

After identification of the mutant gene, the consequences of the 1795insD insertion on the electrophysiological properties of the Na^+ channel were investigated (MWV). Na^+ currents (I_{Na}) were recorded in Xenopus oocytes injected with cRNA encoding either the wild type or the 1795insD mutant Na^+ channel α subunit. The mutant channels were characterised by a markedly reduced I_{Na} amplitude, a positive shift of voltage dependence of activation and a substantial negative shift of voltage dependence of inactivation of I_{Na}.[7] In addition, the mutant disrupted fast inactivation, causing sustained I_{Na} throughout the action potential, thereby delaying repolarisation, and causing slow inactivation, thus delaying recovery of Na^+-channel availability between stimuli further reducing I_{Na} amplitude.[10] The latter feature translates into the clinical observation that the ST segment becomes more elevated at faster rates.

Regarding bradycardia, it appeared that the persistent I_{Na} causes prolongation of the action potential of the sinus node cells, whereas the negative shift in inactivation causes a slowing of the diastolic depolarisation rate, both factors contributing to a reduction in sinus rate.[14]

Treatment

Since the vast majority of patients were asymptomatic, treatment was aimed at preventing sudden death. Patients were advised to refrain from taking agents with known repolarisation-prolonging properties (e.g. certain antibiotics, antidepressants, antihistamines). In addition, although β-blockers are the cornerstone of the treatment of LQTS in general, we considered these agents contraindicated in this family given the combination of nocturnal sudden death, sinus bradycardia and bradycardia-dependent QT prolongation. Instead, we reasoned that anti-brady pacing might be useful. Thus, from 1978 onwards an artificial transvenous cardiac pacemaker for anti-brady pacing was implanted in a number of patients. In each particular patient the decision to implant a pacemaker was based on clinical judgement and patient preference. A pacemaker was considered in cases of profound bradycardia during Holter monitoring, but there were no strict criteria. Data on 30 adults patients who received a pacemaker for prevention of sudden death have been detailed recently.[11] Briefly, patients with a pacemaker were younger at first presentation and had a slightly lower heart rate, but otherwise they were comparable with the 30 patients who did not receive a pacemaker. A VVI pacemaker was used in 17 patients, whereas DDD and AAI pacemakers were used in nine and four patients, respectively. Back-up pacing rate ranged from 50 to 70 beats/min. Mean age at implantation was 36.7±10.0 years. Median follow-up after implantation

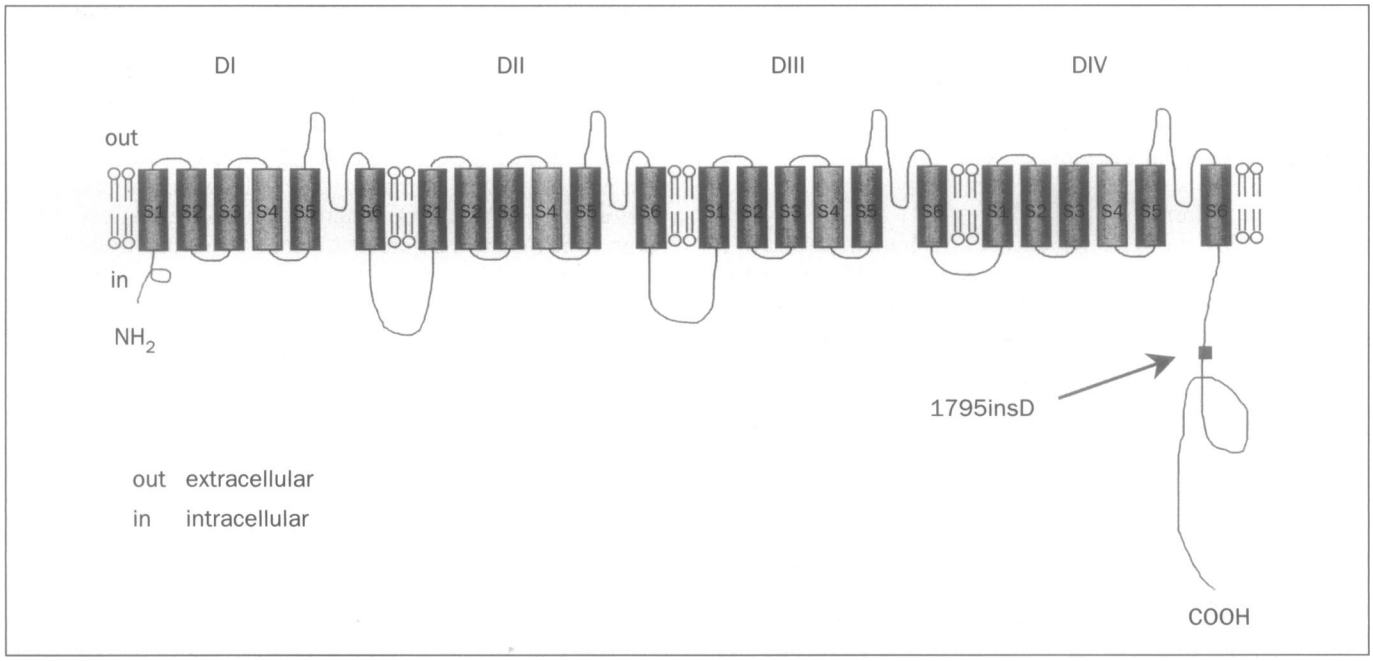

Figure 5. Structure of the cardiac sodium channel showing the location of the 1795insD mutation. The cardiac sodium channel consists of four domains (DI-DIV) each made up of six transmembrane segments (S1-S6). The four domains fold around a central ion-conducting pore, which is lined by the S5-S6 linker (referred to as the P segment or P loop) from each domain. The fourth transmembrane segment in each domain (S4) functions as a voltage sensor. It contains positively charged residues, which bring about motion of S4 segments in response to depolarisation, leading to opening of the channel pore.

was 4.5 (0.0-22.6) years. In this subset of patients in whom a prophylactic pacemaker was implanted, no unexplained sudden death occurred. In contrast, in the 30 patients who did not receive a pacemaker five sudden deaths occurred after 1978. This difference in survival was statistically significant (p=0.019). Based on these favourable results, pacemaker implantation is now a routine prophylactic measure in all patients, with the possible exception of patients without bradycardia after repeated Holter monitoring. Three patients received a pacemaker because of symptoms (see above). Of note, the pacemaker had to be upgraded from AAI to DDD in another patient because of progressive AV block.

Children

Findings in children are currently being analysed. A potential limitation is the fact that heart rate in children is generally higher, thus obscuring bradycardia-dependent QT prolongation. Nevertheless, preliminary data indicated that the clinical diagnosis can already be made at a very young age (1-3 years).[13] In particular, QT prolongation, bradycardia and late potentials were important features. Interestingly, Wenckebach block was also seen more often in carriers than non-carriers.

Genotype-phenoype relation

None of the subjects clinically labelled as non-affected turned out to be a carrier of the mutant gene after genotyping. In the late seventies, three young subjects were suspected of being affected (based on profound nocturnal bradycardia), but they were subsequently demonstrated to be non-carriers. Apart from these three early cases, there was a perfect match between phenotype and genotype. These data indicate full penetrance of the mutant gene.

Discussion

SCN5A, the gene that encodes the human cardiac Na^+ channel α-subunit, is involved in LQT_3, Brugada syndrome and familial conduction system disease (Lenegre's disease).[6,15-17] ECG patterns in these syndromes appear distinct. LQT_3 is characterised by a long iso-electric ST segment preceding a sharp T wave,[18] whereas the typical Brugada ECG consists of an elevated ST segment of normal duration in the right precordial leads.[3,4] Familial conduction system disease is characterised by generalised cardiac conduction delay, which is sometimes progressive. Depending on the specific mutation, combinations of these abnormalities may occur. Thus, conduction defects are often present in both LQT[19,20] and Brugada syndrome.[3,4] Our family is the first to demonstrate the combination of LQT_3 and Brugada syndrome. In addition, since there are obvious conduction defects, the family actually represents the entire spectrum. Moreover, the very large size of the family and the long follow-up are unique.

Within the spectrum of LQTS, LQT_3 represents a small portion (relative prevalence <10%) with distinct features. In addition to the ECG features, provocation of symptoms in patients with LQT_3 is typical; whereas symptoms in the more common forms of LQTS are related to exercise (LQT_1) and sudden arousal (LQT_2), symptoms in LQT3 typically occur at rest or during sleep.[5] The present family also shows these typical features. In addition, by virtue of the very large sample size, several other observations were made, adding to the understanding of LQT_3. An interesting finding is the presence of sinus node dysfunction. Slow rates have also been described in other LQT_3 families,[21,22] but by analysing heart rate variability we were able to prove the presence of intrinsic sinus node dysfunction. Indeed, computational and experimental data indicate that persistent I_{Na} causes prolongation of the action potential of the sinus node cells, whereas the negative shift in inactivation causes a slowing of the diastolic depolarisation rate, both factors contributing to bradycardia. Further, the normal inverse relation between heart rate and QT prolongation is accentuated; unlike patients with LQT_1 and LQT_2, who characteristically exhibit QT prolongation along with increased heart rate,[23] our patients show excessive QT prolongation, especially during slow heart rate. Of note, it may be assumed that the QT prolongation is compounded by the sinus node dysfunction. In other LQT_3 patients[24] and in experimental models mimicking LQT_3[25,26] a fairly steep relationship between action potential duration and QT rate was also observed. The mechanism of QT prolongation seems related to disrupted fast inactivation, typically prolonging cardiac repolarisation at slow rates, as shown for other SCN5A mutants.[22,27] Finally, carriers of the mutant gene are characterised by a paucity of both atrial and ventricular ectopy. In fact, despite extensive Holter monitoring we never observed complex ventricular arrhythmias, but isolated ventricular premature beats were also less common in the carriers compared with the non-carriers.

The family also shares features of the two other SCN5A-linked disorders, i.e. Brugada syndrome and familial conduction system disease. A significant number of carriers display the 'Brugada sign' (ST-segment elevation in the right precordial leads), and the degree of ST-segment elevation can be manipulated by class I antiarrhythmic agents. Further, there is evidence of generalised conduction delay, the cardinal feature of familial conduction system disease. In addition to prolongation of the PR interval and QRS duration, the HV interval was prolonged and many carriers had late potentials.

Whereas in LQT_3 about 20% of all cardiac events are lethal,[28] almost two-thirds of the patients with Brugada syndrome experience (aborted) sudden death as the initial event. In the present family 26 unexplained sudden deaths have thus far occurred. Otherwise, patients were symptom-free, with the exception of only

six patients who experienced syncope. Hence, though an exact figure cannot be given, the lethality of cardiac events appears to be high. Though β-blockers are the cornerstone in the treatment of LQTS in general, we considered these agents contraindicated in the present family given the high incidence of nocturnal sudden death in combination with sinus bradycardia and bradycardia-dependent QT prolongation. Instead, we elected to implant pacemakers for anti-brady pacing as preventive measure against sudden death. This strategy proved to be effective. The combined effect of β-blocker and pacemaker therapy in preventing sudden death was previously reported.[29] Although this approach appeared reasonably effective, sudden death still occurred in a sizeable subset of patients. Unfortunately, patients were not specified according to LQTS subtype (particularly LQT_3). Despite the fact that pacemaker implantation was not randomised, our study is the first to indicate its efficacy in preventing sudden death in a family with LQT_3. However, it remains to be proven whether pacemakers are also efficacious in LQT_3 due to other mutations.

Our observations add to the question of the actual mode of death in this family. Of course, polymorphic ventricular tachyarrhythmia (whether or not bradycardia-induced), in particular torsade de pointes, is a possibility. This possibility is supported by the finding of T-wave alternans in three patients. Also, the observed efficacy of pacemaker treatment may 'simply' be based on prevention of pause-dependent torsade de pointes. However, such arrhythmias were never recorded, nor could they be provoked during acoustic arousal or programmed electrical stimulation. Alternatively, the data suggest the possibility that bradyarrhythmias per se, leading to asystole, may be the ultimate event. Bradyarrhythmias in this instance might be due to both depressed impulse formation (sinus node dysfunction) and conduction delay (at any level) in the absence of an adequate escape rhythm.

In conclusion, we have described a large family with an SCN5A-linked disorder (1795insD) with features of LQT_3, Brugada syndrome and familial conduction system disease. Pertinent features are a high incidence of nocturnal sudden death, bradycardia-dependent QT prolongation, intrinsic sinus node dysfunction, generalised conduction abnormalities, a paucity of ventricular ectopy, and the Brugada sign. Anti-brady pacing was successful in preventing sudden death. The mode of death is possibly bradycardic. ■

Acknowledgements

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