Mortality of Inherited Arrhythmia Syndromes; Insight into Their Natural History

Running title: Nannenberg et al.; Mortality of Inherited Arrhythmia Syndromes

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Abstract

Background - For most arrhythmia syndromes the risk of sudden cardiac death (SCD) for asymptomatic mutation carriers is ill-defined. Data on the natural history of these diseases are therefore essential. The Family Tree Mortality Ratio (FTMR) method offers the unique possibility to study the natural history at a time when the disease was not known and patients received no treatment.

Methods and Results - In six inherited arrhythmia syndromes, caused by specific mutations, we analyzed all-cause mortality with the FTMR method (main outcome measure: Standardized Mortality Ratio (SMR)). In long QT syndrome type 1 (LQTS1), severely increased mortality risk during all years of childhood was observed (1-19 years), in particular during the first 10 years of life (SMR 2.9, 95% CI 1.5-5:1). In LQTS2, we observed increasing SMRs starting from the age of 15 which just reached significance between 30-39 years (SMR 4.0, 95% CI 1.1-10.0). In LQTS3, the SMR was increased between 15 and 19 years (SMR 5.8, 95% CI 1.2-16.9). In the SCN5A-overlap syndrome excess mortality was observed between age 10 and 59, with a peak between 20-39 years (SMR 3.8, 95 % CI 2.5-5.7). In Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), excess mortality was restricted to age category 20-39 years (SMR 3.0, 95% CI 1.3-6.0). In Brugada syndrome, excess mortality was observed between 40-59 years (SMR 1.79, 95% CI 1.2-2.4), in particular in males.

Conclusions - We identified age ranges during which the mortality risk becomes manifest in an unselected and untreated population. This can guide screening of these families.

Key words: arrhythmia, LQTS, Brugada syndrome, CPVT, mortality, FTMR, natural history
Introduction

The molecular genetic substrate of various inherited arrhythmia syndromes has been identified in recent years.1 As a result, an increasing number of mutations in mostly symptomatic probands have been identified. This has facilitated genotyping of family members, and identified mutation carriers before they develop symptoms. In symptomatic untreated patients the risk of sudden cardiac death (SCD) is substantial. However, in asymptomatic mutation carriers the risk is ill-defined. Preventive lifestyle advice may be given, and pharmacological and/or invasive treatment offered. However, such therapies may have side effects and a significant impact on the quality of life.2,3 A number of pressing questions remain unanswered. Should all asymptomatic carriers of a disease-causing mutation be treated? If so, at which age should treatment be started and from what age onward can treatment be safely withheld in asymptomatic patients? What are the optimal genetic and cardiologic screening strategies?

To address these issues data on the natural history of the disease are required. However, they are scarce, because published studies have a strong bias towards symptomatic patients.4 Therefore, we investigated the mortality with the Family Tree Mortality Ratio (FTMR) Method5-7 in six major autosomal dominant inherited arrhythmia syndromes, caused by specific mutations, i.e. long QT syndromes type 1, 2 and 3 (LQTS1, 2 and 3), Brugada syndrome, SCN5A-overlap syndrome (LQTS3/Brugada syndrome/conduction disease)8 and RYR2-gene related Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). This method allows us to study the mortality in times when the disease was not known and therapy was not available, and thus provide information on the natural course of the disease.

LQTS is characterized by a prolongation of the QT-interval on the electrocardiogram (ECG), and associated with ‘Torsades de Pointes’ ventricular tachycardia and ventricular
fibrillation. The estimated prevalence of LQTS is 1:2000. The three most prevalent (sub-) types are LQTS type 1, 2 and 3, caused by mutations in the KCNQ1, KCNH2 and SCN5A genes, respectively. While cardiac events may occur from infancy through middle age, they are most common from the pre-teen years through the 20s. While LQTS1 patients exhibit a high rate of cardiac events during the childhood and adolescence period, the incidence of death is similar in all three types at ~ 4% before the age of 40 years in patients and their relatives.

CPVT is associated with adrenergically-induced ventricular tachyarrhythmias. The first studies on CPVT reported high mortality rates in children. More recent studies, however, showed a later onset of SCD; 30-50% of SCD occurs at age 30-40 years when untreated.

In Brugada syndrome, malignant events can occur at all ages, with a peak around the 4th decade. There is a striking male to female ratio of 8:1.

In the present study, we assessed the mortality of these inherited arrhythmia syndromes, by studying mutation carriers at a time when the disease was not yet known and mutation carriers were untreated.

Methods

Identification of mutation carriers and reconstruction of family trees

We reconstructed large family trees of patients seen in the genetic testing program of inherited arrhythmia syndromes at our cardiogenetics department. For five inherited arrhythmia syndromes (LQTS1, 2, 3, CPVT and the SCN5a overlap syndrome), the first step was to search for sets of at least two clinically affected probands who carried the same mutation. Sets of probands with an (almost) identical haplotype (and a large likelihood of having a distant common ancestor) were selected for further genealogical analysis. Genealogical analysis was
conducted until a shared distant pair of ancestors was identified. Subsequently, family trees were reconstructed by tracing the descendants of these pair of ancestors and including all siblings in each generation. Thus these family trees contained certain (genotyped or obligate) mutation carriers and those with a 50% chance of being a carrier (siblings of certain carriers).

Furthermore, in some pedigrees, the additional transmission lines of the specific mutation through the pedigree were identified by testing living descendents. This way, we reconstructed large family trees of families with the following mutations: c.565G>A (p.Gly189Arg) in KCNQ1 (LQTS1), c.296A>C (p.Tyr99Ser) in KCNH2 (LQTS2), c.5302A>G (p.Ile1768Val) in SCN5A (LQTS3), c.5385insTGA (p.1795insAsp), a Dutch founder mutation in SCN5A (SCN5A-overlap syndrome; LQTS3/Brugada/conduction disease) and c.1258C>T (p.Arg420Trp) in the RYR2 gene (CPVT).

Furthermore, for the Brugada syndrome, we collected 37 small contemporary family trees (the proband with all first degree relatives) with a pathogenic mutation in the SCN5A gene (supplemental Table I). Some family trees were extended, by testing the specific mutation through the pedigree.

Subsequently, from all individuals in the family trees, data on birth and death were obtained from official Dutch archives. In the Netherlands, these data are very well preserved from the beginning of the 19th century and have been collected of all inhabitants.

We excluded all probands, since they had to be alive to visit our cardiogenetics clinic and would therefore introduce bias to years without deaths. The years of life of the parent(s) before birth of the (obligate) mutation carriers were excluded to avoid ‘reproduction’ bias, since they must have been living until this age to transmit the mutation to their offspring. We excluded the first year of life of all individuals from all our analyses, as registration of neonatal mortality in
the 19th century might not have been accurate. We ended all analyses at death, when a diagnosis was made in an individual (and treatment was started) or in the year when the mutation was identified (and presymptomatic testing became available and treatment could have been started). All probands gave informed consent to the study.

Statistics (FTMR method)

The mortality in our family trees (observed mortality) was compared to the mortality of the Dutch general population (expected mortality) standardized for age, sex and calendar period, as previously described.5-7,21,22 The ratio of observed to expected mortality is the standardized mortality ratio (SMR). The expected mortality was calculated by multiplying the total number of years lived by the study population in each calendar period per sex and age category with the age and sex specific mortality rates of the Dutch population for each calendar period, available at ‘Statistics Netherlands’, using the computer program ‘Person-Years’.23 The 95% confidence interval of the SMR was calculated assuming a Poisson distribution of the observed number of deaths and by using exact limits.

We analysed the following arbitrary age categories: from 1-19, 20-39, 40-59, 60-79 and 80-109 years. These 20 years categories were chosen to avoid relatively empty cells and to enable comparison with similar data in literature. In addition, we showed smaller age categories in an inset when (significantly) increased mortality was observed in these specific age categories.
Results

Pedigrees:

Five large family trees were reconstructed, dating back to the 18-19th century (figure 1 and supplemental figures).

Furthermore, 37 small family trees (Brugada syndrome) were reconstructed, containing 508 relatives (246 males and 262 females).

Table I gives an overview of the characteristics of the pedigrees.

Mortality risk (Standardized mortality rates):

LQTS1: between 1811 and 2001 (when the mutation was detected in the family), 45 deaths (between 1-109 years) occurred in 2533 person-years among 59 persons. The overall SMR was 1.5 (95% CI 1.1-2.0). In particular, we observed significant and severe excess mortality in one age category: 1-19 years (SMR 3.0, 95% CI 1.7-5.0; Figure 2a) Additional analyses identified a smaller specific age category in which the excess mortality was significant (figure 2a inset): between 1-9 years (SMR 2.9, 95% CI 1.5-5.1). Between 10-19 years, the SMR was high, but not statistically significant (SMR 3.4, 95% CI 0.7-9.9).

LQTS2: between 1811 and 2003, 25 deaths occurred in 3728 person-years among 78 persons. The mean SMR over that period was 0.9 (95% CI 0.6-1.3), i.e. there was no overall excess mortality. Between 1-14 years, there were no observed deaths. From the age of 15 years, the SMR started increasing (15-19 years SMR 2.6, 95% CI 0.1-14.7). Only between 30-39 years did excess mortality reach significance (SMR 4.0, 95% CI 1.1-10.0) (Figure 2b).
**LQTS3**: between 1811 and 2004, 32 deaths occurred in 2216 person-years among 44 persons. The mean SMR was 1.0 (95% CI 0.7-1.4). When looking at smaller age categories, there was severe excess mortality between 15-19 years (SMR 5.8, 95% CI 1.2-16.9; Figure 2c inset).

**SCN5A-overlap syndrome**: between 1811 and 1998, 92 deaths occurred in 10510 person-years among 308 persons. The SMR was 1.5 (95% CI 1.2-1.8). A closer look revealed that severe excess mortality started after the age of 10 years (category 10-14 years; SMR 9.8, 95% CI 4.2-19.2) and peaked between 20-39 years (SMR 3.8, 95% CI 2.5-5.7). Above 60, no excess mortality was observed (Figure 2d).

**CPVT**: between 1858 and 2004, 36 deaths occurred in 6362 person-years among 173 people. The overall SMR was 1.1 (95% CI 0.8-1.5). In the age category 20-39 years, we observed significant excess mortality (SMR 3.0, 95% CI 1.3-6.0). When looking at smaller age categories (Figure 2e inset), between 20-29 years, the SMR was more severely increased (SMR 3.7, 95% CI 1.2-8.6). Above 40 years, no excess mortality was observed (Figure 2e).

**Brugada syndrome**: between 1877 and 2009, 102 deaths occurred in 22150 person-years. The SMR was 0.8 (95% CI 0.7-1.0). In the age category 40-59 years, we observed significant excess mortality (SMR 1.72, 95% CI 1.2-2.4). When looking at smaller categories, between 40-49 years a SMR of 2 just reached significance (95% CI 1.05-3.4). When looking at gender, in males between 40-59 years the SMR was 2.0 (95% CI 1.2-3.0), in females no excess mortality was observed in any age category (Figure 2f, 2fi, 2fii).
Discussion

For most arrhythmia syndromes it is not well known to what extent asymptomatic carriers are at risk for SCD. At the same time, physicians face an increasing need for data about the natural history, when decisions about preventive measures and screening strategies have to be taken for a rapidly increasing number of asymptomatic gene carriers. The FTMR method offers the unique possibility to study the mortality of inherited arrhythmia syndromes at a time when the disease was not known and patients received no treatment. Unfortunately, the design of our mortality study does not allow extrapolation to the morbidity from these disorders.

We realize that we studied specific mutations in a number of families and that our results cannot be generalized to all families with these inherited arrhythmias. Yet, in syndromes where classes of mutations share pathophysiological mechanisms, FTMR data on one of them may be relevant to a larger group. In line with this, it has been shown that biophysical function, location and type of KCNQ1 mutations are important independent risk factors influencing the clinical course of the disorder\(^{24,25}\) and comparable data as to location and type of KCNH2 mutations have been presented.\(^{26}\) Ideally, more large families should be studied with the FTMR method to obtain evidence if our results can be generalized and consortia should be formed to cluster the data of pedigrees with identical mutations to study the effect of genetic modifiers on the burden of these disorders.

By interpreting our results, one has to take into account that, as a result of analyzing complete sibships (certain carriers and all siblings) in each generation, our estimates express at least 50\% of the excess risk. This implies that the excess mortality in certain carriers is even higher than the increased SMRs that we found. However, if our reported observed SMRs are
(around) 1, the SMR of certain carriers can only also be 1, since the SMR of the general population is 1.

We excluded the first year of life of all individuals from all our analyses, as registration of neonatal mortality in the 19th century might not have been accurate. As a consequence, we could not analyse Sudden Infant Death Syndrome (SIDS). We observed clear excess mortality in our families relative to the Dutch population especially in young age categories in some arrhythmia syndromes. For this reason and because our analysis were based on age specific rates, our analyses are unlikely to have been affected by competing risk (i.e that mortality from other causes, mainly infectious diseases in the past, was so high that people died from other causes before they could die from the arrhythmia syndromes). 27

We identified specific age categories in patients with LQTS1, LQTS2, LQTS3, SCN5A-overlap syndrome, CPVT and Brugada syndrome to which the excess mortality was limited. These age categories compare well from what is known from data on predominantly symptomatic probands. In LQTS1 (caused by the c.565G>A (p.Gly189Arg) mutation), severe increased mortality during childhood was observed (1-19 years), in particular during the first 10 years of life (figure 2a). In LQTS2 (caused by the c.296A>C (p.Tyr99Ser) mutation), we observed increasing SMRs starting from the age of 15 which just reached significance between 30-39 years. In LQTS3 (caused by the c.5302A>G (p.Ile1768Val) mutation), SMR was increased between 15 and 19 years. Taken into account the considerations discussed above, these data (the first to be based on data in times when the disease was not known and therapy was not available) show that our LQTS1 patients are mainly at risk before age 20 (more particular age 10), and LQT2 and 3 patients from puberty onwards. In contrast to children and adolescents, adults above age 40 in our LQTS1, 2, and 3 families had no excess mortality. Persons with the SCN5A-
overlap syndrome demonstrated significant and severe excess mortality between age 10 and 59, with a peak between 20-39 years. In CPVT (caused by the c.1258C>T, p.Arg420Trp mutation in the RYR2 gene) excess mortality was restricted to age category 20-39 years (in particular 20-29 years). In the Brugada syndrome families (caused by multiple mutations), excess mortality was restricted to the age category 40-59, in particular in males.

There is little doubt that the International LQTS Registry of probands and present-day relatives has been instrumental to the current knowledge of the risk of LQTS patients. Genotype-specific risk for symptoms, including aborted cardiac arrest and SCD have been published for different age-categories. Comparable to our FTMR data, LQTS1 patients were reported to have the highest risk of cardiac events during childhood and adolescence, whereas LQTS2 patients maintain a high event rate throughout adulthood. When limited to death (the parameter studied by the FTMR method) of cardiac arrest, LQTS1 patients are also more severely affected before puberty, whereas casualties in the LQTS2 and LQTS3 population are more prevalent during or after puberty. However, in a larger, more recent series of patients, when limited to life-threatening events (aborted cardiac arrest and sudden cardiac death), differences between the three LQTS genotypes was attenuated before the age of 40. Published data suggest a slightly increased risk of life-threatening events above the age of 18, in particular above the age of 40, in all genotypes with a probably more increased risk in LQTS2 and LQTS3 patients. Our data don’t show an increased mortality risk above age 40 (in patients who were untreated before that age). This can be the result of our unselected population: our patients were selected by Mendelian inheritance and not because they had a severe clinical phenotype. Alternatively, it might reflect the specific clinical course of the mutations we studied, as most literature is based on pooled patients with different mutations.
In previous studies on the clinical presentation of CPVT, the mean age of clinical presentation was 8 years. If left untreated, 80% of CPVT patients had developed symptoms (syncope, ventricular tachycardia or ventricular fibrillation) by age 40.\textsuperscript{13-18,31,32} The median age of lethal events was $18\pm8$ years in the study of Priori et al. and 28 years in the study of Postma et al and in a recent study by Hayashi et al a fatal or near fatal event occurred between 13 and 26 years of age.\textsuperscript{16-18} The excess mortality between 20-39 years in our study is on the late end of the age ranges described, but can reflect the specific clinical course of the mutation in this family.

In Brugada syndrome, our data is in line with the existing literature, reporting a peak in malignant events in the fourth decade with predominantly males affected.\textsuperscript{20,33,34}

These data might help to guide treatment and genetic and cardiological screening strategies in families with an inherited arrhythmia syndrome. Our best example, because of its large size, is the family with the SCN5A-overlap syndrome. Based on the increased overall SMR and the mortality per age category, cardiological and genetic screening of the first degree family members of SCN5A-overlap syndrome mutation carriers, is justified from the age of 5 years until the age of 60 (the SMR starts to increase between 5-9 and is significantly increased from the age of 10 until 60 years) Furthermore, implantation of a pacemaker or implantable cardioverter/defibrillator (which is at the moment the standard procedure in mutation carriers),\textsuperscript{35} may be postponed well after the age of 5 year and is not needed after the age of 60 in asymptomatic patients not treated before. In the LQTS families, the high mortality risks at a young age justifies (active) cardiological and genetic screening of the first degree family members of LQTS probands with the described mutations at a very young age, in particular in LQTS1. For the CPVT family studied, the mortality risk below age 20 and above 40 years was not statistically different from the Dutch population. Untreated asymptomatic carriers in this
family, who were identified with family screening, may therefore lack an indication for treatment (β-blockers) above the age of 40 years: hence, our data do not support the advice to always start β-blocker treatment in carriers of the c.1258C>T mutation even when there is no history of cardiac events and without arrhythmias on stress testing.\textsuperscript{36,37} We would like to emphasize that our advice does not account for other CPVT families caused by a different \textit{RYR2} mutation. In Brugada syndrome, the data are pertinent to more than one mutation and accurately follow the known clinical presentation. Hence insight into the mortality of the disease warrants an expectative policy in particular in asymptomatic females in the first 3 decades (with proper lifestyle adjustments, i.e. fighting fever).

In conclusion, we studied (all cause) mortality and quantified the risk for death in the main inherited arrhythmia syndromes by collecting data from a time when these diseases were unknown and patients were not treated for the disease with an unique method (the FTMR method). As such we are able to describe the natural history of these diseases (caused by specific mutations). We identified age ranges during which the risk for lethal events is increased in untreated patients. Our data might help to further guide treatment and screening strategies in an increasing group of (asymptomatic) mutation carriers who are detected by molecular genetic testing in families with an inherited arrhythmia syndrome.

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**References:**


**Table 1.** Family tree characteristics

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<th>50% carriers</th>
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Figure Legends:

**Figure 1.** Family tree with Long QT syndrome type 1 (LQTS1). The probands are indicated with an arrow. Solid squares: 100% (obligate) male carriers; open circles: female with a 50% probability of carrihership; semi-solid squares or circles: male or female with a 50% probability of carrihership (=ancestor pair). The numbers in the open circles or squares indicate the total number of siblings. Crossed of subjects have passed away.

**Figure 2a.** All cause mortality (Standardized Mortality Ratio, SMR) with 95% Confidence Interval (CI) in LQTS1 by age categories (males and females). In the inset, smaller age categories are depicted. **2b.** All cause mortality (SMR) with 95% CI in LQTS2 by age categories (males and females). **2c.** All cause mortality (SMR) with 95% CI in LQTS3 by age categories (males and females). **2d.** All cause mortality (SMR) with 95% CI in SCN5a overlap syndrome by age categories (males and females). **2e.** All cause mortality (SMR) with 95% CI in CPVT by age categories (males and females). **2f.** All cause mortality (SMR) with 95% CI in Brugada syndrome by age categories (males and females). **2fi.** All cause mortality (SMR) with 95% CI in Brugada syndrome by age categories in males. **2fii.** All cause mortality (SMR) with 95% CI in Brugada syndrome by age categories in females.
Figure 2a
Figure 2f

Circulation
Cardiovascular Genetics

SMR

10.00

1.00

0.10

0.01

1 - 19 20 - 39 40 - 59 60 - 79 80 - 109

years

1 10 32 34 25

observed deaths
Figure 2fi

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Online Supplemental Table I. Different mutations in the SCN5A gene

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Supplemental pedigrees.

LQTS2