Low rate of cardiac events in first-degree relatives of diagnosis-negative young sudden unexplained death syndrome victims during follow-up

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BACKGROUND Sudden unexplained death syndrome (SUDS) in young individuals often results from inherited cardiac disease. Accordingly, comprehensive examination in surviving first-degree relatives unmasks such disease in approximately 35% of the families. It is unknown whether individuals from diagnosis-negative families are at risk of developing manifest disease or cardiac events during follow-up.

OBJECTIVE This study aimed to study the prognosis of first-degree relatives of young SUDS victims, in whom the initial cardiologic and genetic examination did not lead to a diagnosis.

METHODS We retrieved vital status of surviving first-degree relatives from 83 diagnosis-negative families who presented to our cardiogenetics department between 1996 and 2009 because of SUDS in ≥ 1 relatives aged 1–50 years. Moreover, we contacted relatives who previously visited our center for detailed information.

RESULTS We obtained detailed information (median follow-up 6.6 years; interquartile range 4.7–9.6 years) in 340 of 417 first-degree relatives (81.5%) from 77 of 83 families (92.8%). Vital status, available in 405 relatives (97.1%), showed that 20 relatives (4.9%) died during follow-up, including 1 natural death before the age of 50. This girl belonged to a family with multiple cases of idiopathic ventricular fibrillation and SUDS, including another successfully resuscitated sibling during follow-up. Two hundred thirty-four of 340 first-degree relatives (68.8%) underwent cardiologic examination. Of these, 76 (32.5%) were reevaluated. Inherited cardiac disease was diagnosed in 3 families (3.6%).

CONCLUSION In first-degree relatives of young SUDS victims with no manifest abnormalities during the initial examination, the risk of developing manifest inherited cardiac disease or cardiac events during follow-up is low. This does not apply to families with obvious familial SUDS.

KEYWORDS Sudden unexplained death syndrome; Sudden cardiac death; Arrhythmia; Genetics

ABBREVIATIONS IVF = idiopathic ventricular fibrillation; **SUDS** = sudden unexplained death syndrome

(Heart Rhythm 2014;11:1728–1732)

Introduction

Sudden death in apparently healthy young individuals is often caused by inherited cardiac diseases.[1,2] Consequently, the risk of cardiovascular disease and ventricular arrhythmias is higher in relatives of young sudden cardiac death victims, in particular relatives younger than 35 years, than in the general population.[3] In approximately 18%[1] (range 6%–35%[2,4–9]) of young sudden death cases, autopsy does not reveal the cause of death, and in many countries, autopsy is not routinely performed in all these fatalities. Sudden unexplained death syndrome (SUDS) is diagnosed in both cases.[10]

Comprehensive cardiologic and molecular genetic evaluation of first-degree relatives of young individuals experiencing SUDS is indicated.[11,12] This evaluation unmasks an inherited cardiac disease, potentially explaining the fatal event, in approximately 35% of the families,[13–16] enabling timely prophylactic treatment.[17]

Relatives of individuals experiencing SUDS in whom the initial comprehensive cardiologic and genetic examination

This work was supported by ZorgOnderzoek Nederland/Medische Wetenschappen (grant 120610013 to Dr van der Werf, Dr van Langen, and Dr Wilde) and the Netherlands Organization for Scientific Research (grant ZonMW-Vici 918.86.616 to Dr Tan). **Address reprint requests and correspondence:** Dr Christian van der Werf, Heart Center, Department of Cardiology, Academic Medical Center, University of Amsterdam, Meiberg-dreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail address: C.vanderwerf@amc.uva.nl.

does not lead to a familiar diagnosis are usually advised to undergo cardiologic reexamination on a regular basis, as inherited cardiac diseases may manifest during follow-up.[10,18,19] Whether cardiologic examination during follow-up unmasks previously undiagnosed inherited conditions and whether these relatives are at risk of SUDS has, to our knowledge, not been studied. Indeed, if relatives of an individual experiencing SUDS are carrier of an undiagnosed inherited cardiac disease, potentially fatal cardiac events could occur during follow-up.

To address these issues, we carried out an observational follow-up study in first-degree relatives of young individuals experiencing SUDS, in whom the initial cardiologic and genetic examination did not lead to a diagnosis.

Methods

Setting

Details on our multidisciplinary cardiogenetics outpatient clinic at the Academic Medical Center, Amsterdam, The Netherlands (teaching hospital)[17] and our SUDS registry comprising families who underwent cardiologic and genetic examination after the diagnosis of SUDS in a relative aged 1–50 years (the proband) have been given.[15] *SUDS* was defined as out-of-hospital natural death in a previously healthy individual whose family had no known inherited cardiac disease, in whom death occurred within 1 hour after the start of complaints or within 24 hours of the victim being seen alive and well, and in whom autopsy was not performed or initially did not explain the death.[15] In our cardiogenetics clinic, relatives of SUDS victims are counseled by both a cardiologist and a clinical geneticist or genetic counselor, who collect detailed information on the proband with SUDS (including circumstances of SUDS) and the family. This is followed by a tailored cardiologic examination and targeted molecular genetic testing. After the completion of these investigations, the relatives receive a letter that summarizes the complete evaluation that was performed in their family. When a diagnosis is made, appropriate follow-up is arranged. When no diagnosis is made (diagnosis-negative family), most relatives are advised to undergo repeated cardiologic evaluation, in particular when they develop possible cardiac symptoms. This advice is individualized and based on the level of suspicion of an inherited cardiac disease and age. For example, children are usually advised to undergo yearly cardiologic evaluation whereas adults are advised to undergo evaluation every 3–5 years.

Study population

This analysis comprised all surviving first-degree relatives (parent, sibling, or child) from diagnosis-negative families of an individual experiencing SUDS aged 1–50 years, of whom ≥ 1 first-degree relatives presented to our cardiogenetics clinic between 1996 and mid-2009.[15]

Follow-up

First, all first-degree relatives who had not visited our center recently were contacted by using a standardized questionnaire to obtain detailed information on themselves and their family. Second, we contacted at least 1 first-degree relative per family by phone for additional questioning, including on non–first-degree relatives. Cardiologic reevaluation, newly diagnosed (inherited) cardiac disease, and the occurrence of cardiac events (defined as aborted cardiac arrest or sudden death) as well as death due to other causes at any age in the family were questioned. In relatives who had visited our center and gave consent for their participation in this study, additional information was obtained from the relative's general practitioner, cardiologist, or hospital records, when necessary. All the relatives who were examined within a year after the family came to our attention were considered to be part of the initial examination. The yield of cardiologic evaluation during follow-up included the yield of cardiologic evaluation in all relatives who were evaluated for the first time ≥ 1 years after the family came to our attention and the yield of reevaluation in relatives who were part of the initial examination.

Information on vital status of first-degree relatives in whom no detailed information could be collected was obtained from the Dutch national population registry and was verified until January 1, 2013. This national population registry does not contain information on the cause of death.

Follow-up durations were counted from the date when the first relative of that family presented to our center to the date when information on a relative or the relative's death was obtained.

Statistical analysis

Continuous data are presented as median (interquartile range) and categorical variables as number (percentage). Descriptive statistics were used for the analysis.

Results

Study population

Ten of 93 (10.2%) families with SUDS who were classified diagnosis-negative SUDS after the first cardiologic examination[15] were excluded from the present analysis: 5 families because only second-degree relatives were examined; 3 who were double counted because it was found, after the initial analysis, that they were related to each other; and 2 because no follow-up information, including vital status, was available in any relative. Hence, we included the first-degree relatives of 83 SUDS victims. Nineteen probands (22.9%) were aged 1–21 years, and autopsy was performed in 40 (48.2%) (Table 1).

At the time of their death, the 83 individuals experiencing SUDS had 417 living first-degree relatives. Detailed follow-up information was available in 63 families (75.9%), comprising 308 first-degree relatives. In 20 families (24.1%), follow-up was incomplete, with detailed follow-up information in 34 relatives, vital status in only 61, and no