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CLINICAL RESEARCH

Improving usual care after sudden death in the young with focus on inherited cardiac diseases (the CAREFUL study): a community-based intervention study

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Aims Inherited cardiac diseases play an important role in sudden death (SD) in the young. Autopsy and cardiogenetic evaluation of relatives of young SD victims identifies relatives at risk. We studied the usual care after SD in the young aimed at identifying inherited cardiac disease, and assessed the efficacy of two interventions to improve this usual care.

Methods and results We conducted a community-based intervention study to increase autopsy rates of young SD victims aged 1–44 years and referral of their relatives to cardiogenetic clinics. In the Amsterdam study region, a 24/7 central telephone number and a website were available to inform general practitioners and coroners. In the Utrecht study region, they were informed by a letter and educational meetings. In two control regions usual care was monitored. Autopsy was performed in 169 of 390 registered SD cases (43.3%). Cardiogenetic evaluation of relatives was indicated in 296 of 390 cases (75.9%), but only 25 of 296 families (8.4%) attended a cardiogenetics clinic. Autopsy rates were 38.7% in the Amsterdam study region, 45.5% in the Utrecht study region, and 49.0% in the control regions. The proportion of families evaluated at cardiogenetics clinics in the Amsterdam study region, the Utrecht study region, and the control regions was 7.3, 9.9, and 8.8%, respectively.

Conclusions The autopsy rate in young SD cases in the Netherlands is low and few families undergo cardiogenetic evaluation to detect inherited cardiac diseases. Two different interventions did not improve this suboptimal situation substantially.

Keywords Sudden death • Sudden cardiac death • Sudden unexplained death syndrome • Genetics • Epidemiology • Autopsy • Family • Prevention

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What's new?

- Inherited cardiac diseases play an important role in sudden death (SD) in the young. Autopsy and cardiogenetic evaluation of relatives of young SD victims identifies relatives at risk. However, studies on the entire care pathway between the occurrence of SD in the young and identification of the victims' relatives at risk of having potentially fatal inherited cardiac diseases are lacking.
- We report on a community-based intervention study to assess and increase autopsy rates of young SD victims aged 1–44 years and referral of their relatives to cardiogenetic clinics to detect inherited cardiac diseases.
- Autopsy was performed in 169 of 390 registered SD cases (43.3%). Cardiogenetic evaluation of relatives was indicated in 76% of cases, but only 8% of these families attended a cardiogenetics clinic.
- Two different interventions did not substantially improve the low autopsy rates and low number of families that undergo cardiogenetic evaluation.

Introduction

The sudden death (SD) of young individuals, albeit rare, prompts full attention of the media and has led to mounting awareness of this health problem. The incidence of SD due to cardiac or unknown causes [sudden cardiac death (SCD)] in persons of 1–35 years of age has been estimated at 1–2 per 100 000 person-years.[1,2] Inherited cardiac diseases, particularly premature coronary heart disease (CHD) and inherited cardiomyopathies, are important causes of SCD.[1–3] In cases that remain unexplained after autopsy [so-called sudden arrhythmic death syndrome (SADS)], cardiogenetic evaluation of first-degree relatives and screening of SADS-associated genes identify inherited cardiac diseases, primarily inherited arrhythmia syndromes, in ~30–50%.[4–8] Recent data suggest that relatives of young SCD victims are also at increased risk of cardiovascular diseases in general as well as cardiomyopathies and ventricular arrhythmias, with young first-degree relatives at the greatest risk.[9] However, up to now, little attention has been paid to a universal, structured diagnostic approach after the SCD of a young person to identify possible relatives who are carrier of an inherited cardiac disease that predisposes to SCD.[3] Such an approach should consist of good-quality autopsy, including storage of DNA, and timely referral of relatives for cardiologic or, preferably, multidisciplinary cardiogenetic evaluation when an inherited cardiac disease is suspected or cannot be excluded.[3,10] The rationale of this recommendation is that in relatives found to be carriers of a potentially fatal condition, the risk of SCD can be decreased by life style modification, medication or, if indicated, pacemaker or implantable cardioverter-defibrillator implantation. However, in many countries, this approach is neither part of any guideline nor universally known to or applied by physicians involved in young SCD cases.[11]

This study was undertaken to gain insight into the entire care pathway between the occurrence of SD in the young and identification of the victims' relatives at risk of having potentially fatal inherited cardiac diseases.[12] Our primary objectives were to study the usual processes of care after the SD of young individuals aimed at identifying an inherited cardiac disease as the cause of death (i.e. autopsy and cardiogenetic evaluation of first-degree relatives), and to test the efficacy of two interventions to improve this usual care.

Methods

Study design

The yield of CARdiogenetic scrEening in First-degree relatives of sudden cardiac and UnexpLained death victims <45 years (CAREFUL) study was a prospective community-based intervention study designed to monitor the usual care after SD of individuals aged 1–44 years and to test the efficacy of two interventions. The design has been described in detail previously.[12] In brief, the study was performed in two intervention and two control regions of the Netherlands, comprising 2 843 901 inhabitants aged 1–44 years, covering 30.8% of the Dutch population in this age group.[13] The study population consisted of SD cases identified between 1 June 2008 and 31 May 2011, and their first-degree relatives. The Medical Ethics Committee of St Antonius Hospital, Nieuwegein, the Netherlands, approved the study protocol and granted exemption of the requirement of written informed consent for collection of information about the deceased. All relatives who visited the cardiogenetics clinics consented to storage of information into the Dutch national registry for patients and families with familial heart diseases (GENCOR).[14]

Definitions

We sought to include cases of sudden unexpected death from natural causes following cardiac arrest that occurred out-of-hospital or in the emergency room. Based on recent studies and recommendations,[3,15] we decided to narrow the definition of *sudden*[11] for the present analysis to the following: in resuscitated individuals *sudden* was defined as cardiac arrest that occurred within 1 h of the onset of acute cardiovascular symptoms. Unwitnessed deaths were included when the victim was seen alive and apparently well within 24 h previously. Cases in which these time definitions could not be assessed were excluded.

Death was considered *unexpected* if terminal illness was absent. The cause of death was considered natural in the absence of the suspicion of a non-natural cause. Because toxicology screening is not routinely performed in the Netherlands, the coroner's judgment on whether death was due to a drug or medication overdose was followed.

Causes of death were categorized into cardiac causes (definite or probable diagnosis made by autopsy or cardiac diagnostic tests before the victim expired), non-cardiac causes [definite or probable diagnosis made by autopsy, imaging modalities, or clinically (e.g. anaphylactic shock or hyperglycaemia) or through inspection of the corpse (in particular gastrointestinal haemorrhage)], SADS, and unspecified cases (cases in which no autopsy was performed and the cause of death could not be determined by reviewing the clinical data). In autopsied cases, the diagnoses of hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and myocarditis required histopathological confirmation. All fatalities due to cardiac or unspecified causes and SADS cases were considered SCD.

Cardiogenetic evaluation of the victim's relatives was considered indicated in case of unexplained death (both autopsied and non-autopsied cases)[4] and in the following definite or possible inherited cardiac diseases: HCM, inherited or idiopathic dilated cardiomyopathy (DCM), ARVC, restrictive, non-compaction and unclassified cardiomyopathy, unexplained cardiac hypertrophy not meeting the histopathological criteria of HCM, CHD with evidence of premature atherosclerosis, and aortic dissection.

In case of SADS, the cardiogenetic evaluation was focused on the presence of inherited arrhythmia syndromes.[5]

Usual care and interventions

Usual care after the SD of a young individual in the Netherlands has previously been described.[12] In brief, emergency medical service (EMS) paramedics, general practitioners and medical specialists may be involved, depending on the location of the event and whether resuscitation is attempted. When a non-natural cause of death is suspected, a coroner is contacted to inspect the corpse, and the public prosecutor may request judicial autopsy. When death is natural and no judicial autopsy is performed, the treating physician may ask permission from the next of kin for clinical autopsy. Evaluation of the relatives at a cardiogenetics clinic or by a cardiologist may be initiated by the relatives (self-referral) or by the GP or treating medical specialist.

Two different interventions were implemented in the two study regions to stimulate the performance of autopsy and the referral of relatives for cardiogenetic evaluation.[11] In the Amsterdam study region, a central 24/7 study telephone number and a dedicated website were introduced and promoted during the first 6 months among GPs and coroners. These were aimed at providing detailed information on the importance and practicalities of performing post-mortem investigation and the referral of relatives to a cardiogenetics clinic. In the Utrecht study region, GPs and coroners were informed on the same aspects by a letter and educational meetings during the first 6 months. Emergency medical service paramedics were instructed to leave an information letter for physicians involved in a resuscitation attempt of a young individual. In the two control regions (Groningen and Leiden) usual care was monitored.

Outcome measures

The primary outcome measures were autopsy rates and the proportion of families attending a cardiogenetics clinic. Secondary outcome measures were the proportion of families attending a cardiologist, the total proportion of families attending a cardiogenetics clinic or cardiologist, and the proportion of families attending a cardiogenetics clinic within 1 year.

Data collection and classification

To ensure a comprehensive registration of all possible SD cases, including resuscitated individuals and individuals in whom no cardiopulmonary resuscitation was performed because they were clinically dead, we systematically collected the data of all deaths 1–44 years of age from EMS and coroners. All EMS and the coroners in the study regions participated, except for one coroner's office comprising 7.1% of the population at risk. In the Amsterdam study region, EMS cases were collected through the ARREST (Amsterdam Resuscitation Studies) database.[16] In other regions, we verified the outcomes of resuscitated individuals from the EMS reports. All reports on coroners' corpse inspections were collected at the regional departments of Forensic Medicine of the Public Health Services.

In possible cases of SD, GPs were contacted after a minimum of 6 months (to avoid interference with the timely referral endpoint) for additional information on the victim's medical history and the performance of autopsy, and anonymous information on family evaluation. Data on clinical autopsies were verified with the nationwide PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) pathologic network and registry in the Netherlands.[17] Data on judicial autopsies were verified by use of the Netherlands Forensic Institute database, but details on the exact (natural) cause of death were not disclosed.

Six of eight Dutch cardiogenetics clinics, including all clinics from the study regions, provided information on first-degree relatives that were referred for cardiogenetic evaluation. Information on cases of whom DNA was stored, but in which the relatives never attended a cardiogenetics clinic was unavailable.

Information on all possible SD cases was evaluated independently by two investigators (C.v.d.W. and A.H.), to identify cases that met our inclusion criteria. In case of disagreement, an adjudication committee consisting of a cardiologist, a cardiovascular pathologist, a clinical geneticist, and a general practitioner was consulted to reach consensus.

Statistical analysis

Continuous variables are presented as medians [interquartile ranges (IQR)], and categorical variables as proportions or risk ratios and 95% confidence intervals (95% CIs). Outcome measures were compared between the intervention and control regions, and between the two intervention regions. Comparisons between categorical variables were evaluated with Fisher's exact test. Population-based incidence rates were calculated as the proportion of events divided by the number of person-years at risk (95% CI). A *P*-value of <0.05 (two-sided) was considered to indicate statistical significance.

A power calculation based on the proportion of relatives referred to a cardiogenetics centre shows that with the inclusion of 300 SD cases, with a two-sided alpha, 95% power, we would be able to detect a significant difference of at least 5.8% between the control and intervention regions.

Results

Study population and incidence

During the study period, 3552 deaths occurred among individuals 1–44 years of age, of which we identified 1826 out-of-hospital deaths. Of these, 390 cases (21.4%) met the inclusion criteria, covering 11.0% of total mortality in the 1–44-year age group (*Figure 1*). Their median age was 38 years (IQR, 29–41 years) and 274 (70.3%) were male (*Table 1*). Medical history was available in 338 of 390 cases, of whom 134 (39.6%) were ostensibly healthy (*Table 2*).

The annual incidence rate of SD in persons aged 1–44 years in the Netherlands was 4.6 per 100 000 person-years (95% CI, 3.8–5.4). Among previously healthy cases, the incidence rate was 1.6 per 100 000 person-years (95% CI, 1.1–2.0). The incidence of SCD was 3.7 per 100 000 person-years (95% CI, 3.0–4.4) in the entire study population, and 1.2 per 100 000 person-years (95% CI, 0.8–1.6) in previously healthy cases.

Autopsy and cause of death

Table 3 displays the causes of death in autopsied and non-autopsied cases. Autopsy was performed in 169 of 390 cases (43.3%). Autopsy was performed more frequently in cases with no medical history than in cases with a relevant medical history (59.7 vs. 37.3%; $P < 0.001$). Of the 23 events on sports fields or related to exercise, 17 (73.9%) events were autopsied. Of the 14 events occurring with emotion, only 5 (35.7%) events were autopsied.

Among autopsied cases, SD was attributed to a structural cardiac cause in 94 cases (58.0%) and to a non-cardiac cause in 46 cases (28.4%). Sudden arrhythmic death syndrome was present in 22 cases (13.6%). Definite or possible inherited cardiac diseases were present in 108 autopsied cases (63.9%). Among the non-autopsied cases, the underlying cause remained unspecified in the majority of cases (172 of 221; 77.8%).

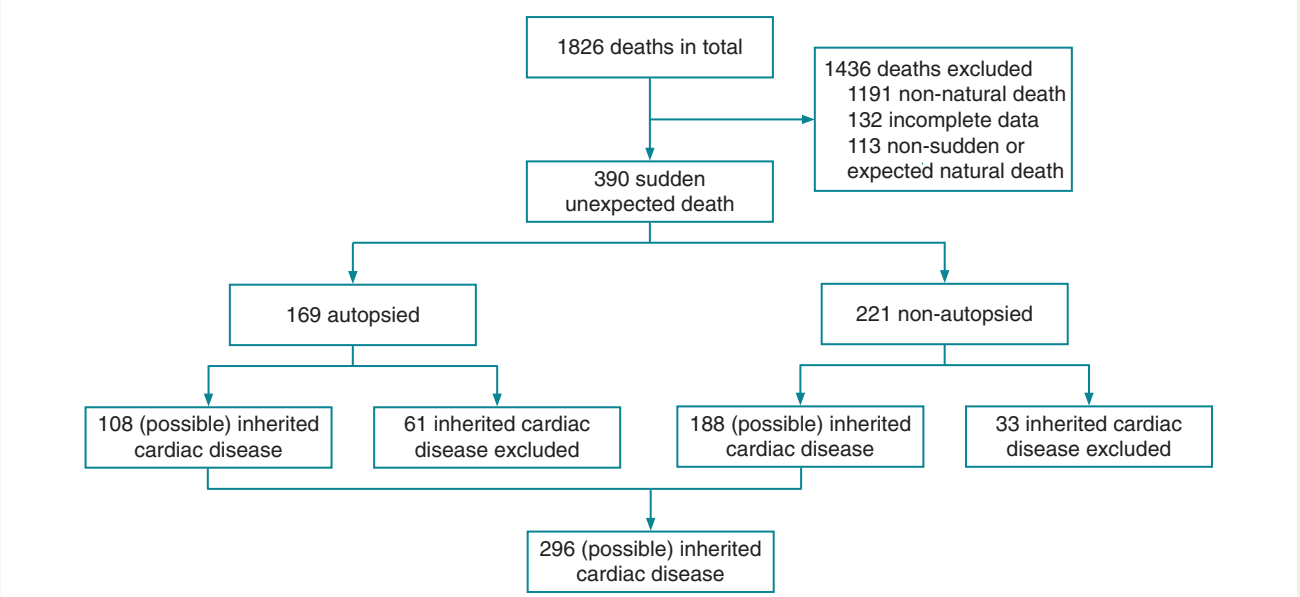

Figure 1 Flow chart of inclusion of SD cases due to natural causes in individuals aged 1–44 year.

Table 1 Characteristics of young SD victims

Characteristic	All (n = 390)	Amsterdam region (n = 173)	Utrecht region (n = 121)	Control regions (n = 96)
Sex, no. (%)				
Men	274 (70.3)	127 (73.4)	87 (71.9)	60 (62.5)
Women	116 (29.7)	46 (26.6)	34 (28.1)	36 (37.5)
Age, median (IQR), years	38 (29–42)	39 (29–42)	37 (31–42)	37 (25–42)
Age categories, no. (%)				
1–9 years	19 (4.9)	9 (5.2)	6 (5.0)	4 (4.2)
10–19 years	25 (6.4)	9 (5.2)	7 (5.8)	9 (9.4)
20–29 years	67 (17.2)	31 (17.9)	16 (13.2)	20 (20.8)
30–39 years	130 (33.3)	51 (29.5)	53 (43.8)	26 (27.1)
40–44 years	149 (38.2)	73 (42.2)	39 (32.2)	37 (38.5)
Medical history, no. (%)[a]				
Relevant medical history	204 (60.4)	81 (57.9)	70 (62.5)	53 (61.6)
Previously healthy	134 (39.6)	59 (42.1)	42 (37.5)	33 (38.4)
Location of event, no. (%)[b]				
Home	261 (68.9)	111 (66.1)	85 (71.4)	65 (70.7)
Street	30 (7.9)	17 (10.1)	9 (7.6)	4 (4.3)
Sports field	14 (3.7)	5 (3.0)	6 (5.0)	3 (3.3)
Other public location	41 (10.9)	26 (15.5)	8 (6.7)	7 (7.6)
Other	33 (8.7)	9 (5.4)	11 (9.2)	13 (14.1)
Circumstances of event, no. (%)[c]				
Rest	129 (49.4)	51 (44.3)	46 (54.8)	32 (51.6)
Sleep	86 (33.0)	43 (37.4)	22 (26.2)	21 (33.9)
During/after exercise	21 (8.0)	9 (7.8)	8 (9.5)	4 (6.5)
Emotion	14 (5.4)	6 (5.2)	5 (6.0)	3 (4.8)
Other	11 (4.2)	6 (5.2)	3 (3.6)	2 (3.2)

[a]Data available in 338 cases.
[b]Data available in 379 cases.
[c]Data available in 261 cases.

Table 2 Details on the SD victims' medical history

Medical condition	Young SD victims ($n = 338$) No. (%)
Previously healthy	134 (39.6)
Cardiovascular risk factors[a]	51 (15.1)
Chronic drug and/or alcohol abuse	47 (13.9)
Heart disease	41 (12.1)
Acquired cardiovascular disease	23 (6.8)
Congenital heart disease	13 (3.8)
Inherited heart disease	6 (1.8)
Psychiatric disease	25 (7.4)
Other neurologic disease than epilepsy	25 (7.4)
Epilepsy	24 (7.1)
Pulmonary disease	16 (4.7)
Chronic or severe acute infectious disease	14 (4.1)
Chronic auto-immune disease	8 (2.4)
Cancer	7 (2.1)
Other	32 (9.5)

Total percentage exceeds 100, because the same individual may fall into different categories.
[a]Cardiovascular risk factors include diabetes mellitus, hypertension, hypercholesterolaemia, and obesity.

Evaluation of first-degree relatives

Cardiogenetic evaluation of the victim's relatives was indicated in 296 cases (75.9%; *Figure 1*). Overall, 42 of 296 families (14.2%) were examined for the presence of inherited cardiac disease. Of these, 25 families (8.4%) visited a cardiogenetics clinic (*Table 4*). Out of a median of 4 first-degree relatives, a median of 2 were examined, and first-degree relatives from 18 families (72%) presented within 1 year after the SD event. Eight first-degree relatives from six families were found to be risk carriers: ARVC ($n = 2$), HCM ($n = 2$), including one with genotype-positive phenotype-negative HCM in whom the deceased had been diagnosed with HCM recently, HCM/non-compaction cardiomyopathy overlap phenotype ($n = 2$), premature atherosclerosis ($n = 1$), and Ehlers-Danlos syndrome type 4 ($n = 1$).

First-degree relatives from 17 families (5.7%) were examined by a cardiologist only. Details were available in seven families: in two relatives from one familial hypercholesterolaemia was diagnosed and one relative from another family was diagnosed with DCM. In the remaining five families, the cardiologic examination was unremarkable.

Overall, an inherited cardiac disease was diagnosed in 8 of 32 [25% (95% CI, 10–40%)] families.

Interventions

In the Amsterdam study region, the central 24/7 study telephone number was contacted 19 times in 3 years. However, only eight contacts concerned persons who had deceased within 24 h of the conversation. The other contacts mainly concerned GPs who wanted to refer persons from their practice with a family history of SCD for to a cardiogenetics clinic.

Table 3 Causes of SD in autopsied and non-autopsied cases

Causes	Autopsied cases ($n = 162$)[a]	Non-autopsied cases ($n = 221$)
Cardiac causes, no. (%)	94 (58.0)	18 (8.1)
CHD	53 (32.7)	10 (4.5)
Myocarditis	14 (8.6)	–
Idiopathic left ventricular hypertrophy	6 (3.7)	–
Unclassified cardiomyopathy	6 (3.7)	–
Idiopathic DCM	5 (3.1)	1 (0.5)
Aortic dissection	3 (1.9)	2 (0.9)
Attributed to pre-existing inherited cardiac disease	–	3 (1.4)
Attributed to pre-existing non-inherited cardiomyopathy	–	2 (0.9)
Other[b]	7 (4.3)	–
Non-cardiac causes, no. (%)	46 (28.4)	31 (14.0)
Intracranial haemorrhage	11 (6.8)	10 (4.5)
Pulmonary embolism	7 (4.3)	3 (1.4)
Pneumonia	6 (3.7)	–
Gastrointestinal haemorrhage	–	6 (2.7)
Hyperglycaemia	–	3 (1.4)
Other	22 (13.6)	9 (4.1)
Unexplained (presumed primary arrhythmia), no. (%)	22 (13.6)	–
Unspecified, no. (%)	–	172 (77.8)
In patients with epilepsy	–	14 (6.3)

[a]Autopsy reports were not available in seven cases.
[b]Other cardiac causes (all identified in one case): HCM, ARVC, hypertensive cardiomyopathy, non-compaction cardiomyopathy, DCM/arrhythmogenic cardiomyopathy overlap, inherited DCM, and no other abnormalities than the patient's known congenital heart defect (surgically corrected ventricular septal defect, transposition of the great arteries and interrupted aortic arch.

Autopsy rates were similar between all regions: 38.7% in the Amsterdam study region, 45.5% in the Utrecht study region, and 49.0% in the control regions (*Table 5*). The proportion of families that were examined at a cardiogenetics clinic was 7.3% in the Amsterdam study region, 9.9% in the Utrecht study region, and 8.8% in the control regions (*Table 5*). Similar results were also obtained for both the total number of families examined for the presence of inherited cardiac disease and the number of families examined by a cardiologist only (*Table 5*). Altogether, no significant differences in outcomes were observed when comparing both interventions, nor when comparing the intervention and control regions.

Discussion

In this community-based intervention study, autopsy was performed in nearly half of cases of SD in the young. Cardiogenetic evaluation of the victim's relatives was indicated in three-quarters of cases, but only

Table 4 Cardiogenetic evaluation of first-degree relatives

Family number	Deceased					First-degree relatives				
	Age	Sex	Medical history	Autopsy	DNA stored	Total number	Number evaluated	Result	Number certainly at risk/possibly at risk/certainly not at risk/unknown risk[a]	Time to attendance (months)
1	39	m	Acromegalia due to pituitary tumour	Hypertrophy and patchy fibrosis	No	6	5	No abnormalities	0/5/0/1	2
2	44	m	No	DCM	Yes	3	2	No abnormalities	0/2/0/1	6
3	41	m	HCM	No	Yes	5	1[b]	Genotype-positive, phenotype-negative HCM	1/0/0/4	2.5
4	40	f	No	CHD	No	4	2	No abnormalities (incomplete evaluation)[c]	0/0/0/4	2
5	16	m	No	Hypoplastic LCX, focal myocardial disarray	Yes	4	4	No abnormalities	0/4/0/0	3.5
6	22	m	No	No abnormalities	Yes	5	2[d]	No abnormalities	0/2/0/2	12
7	42	m	Unstable angina pectoris	Severe coronary artery disease and left ventricular hypertrophy	No	3	2[e]	Premature atherosclerosis	1/0/0/2	7
8	39	m	No	Possible HCM	Yes	2	1	No abnormalities	0/1/0/1	3.5
9	42	m	Hypertension	CHD	No	7	3	No new abnormalities[f]	0/3/0/4	3
10	18	m	Small ventricular septal defect, possible Noonan syndrome	HCM in Noonan syndrome	Yes	4	4	No abnormalities	0/4/0/0	13.5
11	40	m	Mild mental retardation, drug abuse	Arrhythmogenic cardiomyopathy	Yes	3	1	No abnormalities	0/1/0/2	4
12	29	m	No	Lymphocytic myocarditis and possible HCM	No	3	2	No abnormalities	0/2/0/1	NA[g]
13	36	f	No	Arrhythmogenic cardiomyopathy	Yes	6	2	Arrhythmogenic cardiomyopathy	2/0/1/3	4
14	17	m	Atrial fibrillation	No	Yes	5	1	No abnormalities[h]	0/1/0/4	NA[h]
15	5	m	No	No (cerebral imaging unremarkable)	Yes	4	2	No abnormalities	0/2/0/2	7.5

16	18	m	Atrial septal defect, idiopathic pericarditis	Aortic dissection	Yes	4	4	Ehlers-Danlos syndrome type 4	1/0/0/3[b]	3
17	32	m	No	Possible HCM (slight hypertrophy and disarray, not evident), no other abnormalities	Yes	7	2	HCM	1/0/1/5	8
18	38	f	No	No abnormalities	No	6	6	Non-diagnostic abnormalities[i]	0/6/0/0	25
19	43	m	No	Acute myocardial infarction due to LAD occlusion	No	2	2	No abnormalities	0/2/0/0	2
20	42	m	No (examined by cardiologist because of chest pain, no evidence of CHD)	LVH, previous ischaemic lesions, severe trivascular CHD	No	7	2	HCM/NCC	2/0/0/5	NA[j]
21	26	f	No (pregnant)	Aortic dissection	Yes	Unknown	0[k]	NA	Unknown	4
22	41	m	Depression	No abnormalities	Yes	3	1	No abnormalities	0/1/0/2	7.5
23	44	m	No	No abnormalities	No	3	Unknown[l]	Unknown[l]	Unknown[l]	36
24	10	f	No	NCC	Yes	6	2	No abnormalities	0/2/0/4	6.5
25	36	m	No	No abnormalities	Yes	4	2	No abnormalities	0/2/0/2	3
Total	Median: 38 (range, 5–44)	m: 20 (80%)	No medical history: 16 (64%)	Autopsy: 22 (84%)	Yes: 16 (64%)	Median: 4 (range, 2–7)	Median: 2 (range, 1–6)	Abnormalities: 6 (24%)	Total: 8/40/2/52	Median: 4 (range, 2–36); within 1 year: 18/25 (72%)

HCM, hypertrophic cardiomyopathy; CHD, coronary heart disease; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; LAD, left anterior descending coronary artery; LVH, left ventricular hypertrophy; NCC, non-compaction cardiomyopathy.

[a]Definitions: certainly at risk: relatives in whom an abnormality is identified which is certain or likely to be related to the SD event; possibly at risk: relatives with abnormalities that are possibly related to the SD event or relatives in whom carriership of an inherited cardiac disease could not be excluded (e.g. in young children); certainly not at risk: relatives who are certainly a non-carrier of the abnormality identified in their family; unknown risk: non-evaluated relatives or relatives in whom evaluation is still in progress.

[b]Other first-degree relatives refused genetic testing.

[c]Referred from outpatient clinic for cardiogenetics to outpatient clinic for premature atherosclerosis, but did not attend.

[d]Parents underwent ajmaline testing; parents and children did not show up for additional cardiologic evaluation.

[e]One relative was referred to outpatient clinic for premature atherosclerosis, but did not attend.

[f]Two relatives were already known by a cardiologist, one was examined after the SD event.

[g]Both first-degree relatives were cardiologically examined for other reasons before the SD event. This family came under our attention, because a third-degree relative attended our cardiogenetics department because of palpitations in addition to two young sudden cases in her family.

[h]This family presented to a cardiogenetics department before the proband died because of familial atrial fibrillation in the proband and the father.

[i]One relative had "mild arrhythmias", another relative had a decreased LVEF of 40%.

[j]Family examination was ongoing when the SD event occurred because of multiple SCD cases and possible HCM/NCC.

[k]Husband was counselled and genetic testing was performed in the deceased patient; daughter was too young to be examined.

[l]Cardiologic evaluation is ongoing.

Table 5 Autopsy and family evaluation rates in intervention and control regions

Endpoint	Amsterdam study region	Utrecht study region	Control regions	Intervention regions vs. control regions			Amsterdam study region vs. Utrecht study region		
				Risk ratio	95% CI	*P*-Value	Risk ratio	95% CI	*P*-value
Autopsy, no./total no. (%)	67/173 (38.7)	55/121 (45.5)	47/96 (49.0)	0.85	0.66–1.08	0.24	0.85	0.65–1.12	0.28
Family evaluation, no./ total no. (%)	17/137 (12.4)	16/91 (17.6)	9/68 (13.2)	1.09	0.55–2.17	0.99	0.71	0.38–1.32	0.34
Cardiogenetics	10/137 (7.3)	9/91 (9.9)	6/68 (8.8)	0.94	0.39–2.27	0.99	0.74	0.31–1.75	0.63
Cardiologist	7/137 (5.1)	7/91 (7.7)	3/68 (4.4)	1.39	0.41–4.70	0.77	0.66	0.24–1.83	0.58

8% of these families presented for cardiogenetic evaluation. An inherited cardiac disease was diagnosed in a quarter of these families. The interventions that were executed to stimulate the performance of autopsy and the referral of relatives for cardiogenetic evaluation were not effective.

Why were the autopsy rates low?

Autopsy is not mandatory in most countries, and national or local regulations importantly influence autopsy rates.[18] For example, in Denmark a standardized forensic autopsy, including toxicology screening, is to be performed in all cases where the cause of death is not established after external examination. This result in a high autopsy rate of 75% in young SD cases.[2] In the USA autopsy regulations vary among the states. In two recent US studies on SCD in young individuals, autopsy rates were ~70%.[1,19] In the Netherlands and its surrounding countries, a judicial autopsy is performed only when the physician who performed the external examination of the corpse cannot rule out a non-natural cause of death. Clinical autopsy is initiated at discretion of the physician involved, who has to be aware of this possibility and the pros and cons of performing a clinical autopsy, and has to convince the victim's next of kin to obtain consent.

To gain further insight into the lower autopsy rates as observed in the present study, we performed a focus group study of GPs and coroners.[20] The participants indicated that requesting the relatives of the victim permission to perform a clinical autopsy is sometimes hampered by the absence of reimbursement of costs of transporting the corpse to the pathologist. In addition, it may be difficult to arrange the logistics to have a clinical autopsy performed outside business hours, GPs on call may find it emotionally difficult or may not have or take time to discuss the possibility of clinical autopsy with the relatives, especially if these relatives are not their own patients. Moreover, some GPs were not convinced by the diagnostic value of autopsy, based on their own or their colleagues' experiences.

Why were only few families further evaluated?

Appropriate multidisciplinary cardiogenetic evaluation is recommended for all first-degree relatives of individuals that died due to a (potentially inherited) cardiac cause that was identified post-mortem and of SADS cases.[3,10] When autopsy is not performed, family evaluation may also be considered because a genetic cause cannot be excluded beforehand. In one study, the yield of evaluation in first-degree relatives of SADS cases and non-autopsied sudden unexplained death syndrome cases was similar.[4] An adequate nationwide introduction of cardiogenetic evaluation of all relatives with a possible increased risk of SCD may lead to a high level of community detection of inherited cardiac diseases, as recently suggested regarding detection of long QT syndrome patients in New Zealand.[21] In the present study, some of the families at risk were evaluated by a cardiologist, only a few families were evaluated at a cardiogenetics clinic, and when they did, the delay between the fatal event and relatives' first visit was sometimes over 1 year. In our focus group study,[20] GPs indicated that insufficient knowledge regarding the (inherited) causes of SD in the young and preventive options in risk carriers hampered the initiation of family evaluation. In addition, participants indicated that pathologists who performed the autopsies sometimes provide insufficient information, i.e. whether the cause of death identified can (potentially) be genetic. Finally, they mentioned that relatives seem sometimes insufficiently motivated to attend a cardiogenetics clinic. Although the number of examined families was low, the yield of cardiogenetic or cardiologic evaluation in this community-based and unselected population was 25%, again underscoring the importance of offering family evaluation. In the Netherlands, cardiologic and genetic examination of relatives of deceased victims is entirely covered by their health insurance.

Implications

The CAREFUL study indicates that current post-mortem assessment of young SD cases and their relatives focused on inherited cardiac diseases in the Netherlands is poor. Two interventions to improve this situation were largely ineffective. We believe that autopsy and DNA storage rates can only be increased when autopsy is mandatory in all cases of SD without an evident cause of death. In countries with mandatory autopsies, the rates are indeed higher, which does not imply that referral to cardiogenetic screening is an automatism for relatives of suspected cases. Therefore, this should be followed by offering cardiogenetic evaluation to the first-degree relatives when an inherited cause of death is suspected or cannot be excluded.

Internationally, several successful examples of such regulations have been described. In Ontario (Canada), coroners are mandated to investigate every sudden unexpected death and thereby have

the legal right to perform an autopsy. In 2008, 174 young SCD cases with comprehensive information about the event and the cause of death were registered in Ontario. Unfortunately, details on family evaluation were not provided.[22] In the UK, a coroner system similar to Ontario exists. In addition, the National Health Service is required to provide a dedicated cardiogenetics clinic to assess SADS families.[23,24] Although these two system seem an important step forwards in the post-mortem assessment of young SD victims and their relatives, there is still room for improvement by defining referral pathways from the coroner to the GP and cardiogenetics clinics.[25]

In October 2012, the Dutch government introduced new regulations on adequate post-mortem assessment of paediatric victims (<18 years), including an autopsy that could be imposed by a judge when other examinations have failed to identify the cause of death.[26] Although this assessment was effective in identifying the cause of death in the first 40 cases (including 25% of unexplained death), organizational barriers and a significant exceeding of the budget made the government decide to discontinue this assessment as from 2014. Since the implementation of these regulations failed, introducing an easy accessible guideline for medical professionals involved in young SD cases may be helpful, although implementation could still be problematic due to the low incidence rate of SD cases in the young. Finally, when the next of kin do not give permission for a clinical autopsy, a virtual autopsy by means of post-mortem imaging may be suggested.

A drawback of a mandatory post-mortem assessment of young SD cases may be the intrusion into the relatives' personal autonomy and right to decline this assessment. The aforementioned assessment of paediatric fatalities consisted of a quick and thorough protocol, including non-invasive diagnostic tests and psychosocial support for the victim's relatives. When the cause of death remained unknown and the parents decline an autopsy, a judge decided whether the relatives can be overruled. In our opinion, this is an elegant protocol that also respects the relatives' personal autonomy. In a report evaluation the first year of this assessment, most parents of deceased children who underwent this procedure gave positive feedback.

Strengths and limitations

The strengths of this study include its prospective design, its community-based nature, and its use of multiple data sources to detect all SD cases during the study period and to obtain comprehensive clinical information on the victims and their relatives. Additionally, to the best of our knowledge, this study is among the first to provide a community-based insight into the care pathway from the sudden unexpected death of a young person to the identification of the victims' relatives at risk of carrying potentially fatal inherited cardiac diseases. Compared with other studies, this study provids detailed information on the quality of healthcare, beyond incidence rates and causes of death.[1,2] Moreover, the population-based registration of cases reduces the risk of selection bias among families that underwent cardiogenetic evaluation when compared with other studies on cardiogenetic evaluation of SD families in specialized centres.[4,5]

The study had several limitations. Despite the comprehensive data collection, the lack of a nationwide mandatory reporting system for SD may have resulted in failure to detect all relevant cases. It was not possible to retrospectively collect pre-intervention data in the intervention regions, so changes-over time could not be monitored. Furthermore, we were unable to obtain complete clinical data on 132 cases that possibly met our inclusion criteria, the medical history of 52 included cases, and the autopsy reports of 7 cases. Given the relatively small number of missing data this will probably not influence our results. Moreover, the number of families that were evaluated by a cardiologist is probably underestimated, because we did not obtain complete information from all the victims' GPs. Furthermore, data on cases in which DNA was stored (during resuscitation or autopsy), but in which the relatives never attended a cardiogenetics clinic and data of first-degree relatives that possibly visited two cardiogenetics clinics, which were outside the study regions, were unavailable. Finally, autopsy was performed according to local protocols instead of a universal protocol, expert cardiac pathologists were rarely consulted, and toxicology screening was rarely performed, thus, cardiac and non-natural deaths may have remained unidentified.

Conclusions

Current percentages of post-mortem studies of young SD cases and referral for risk assessment in their relatives focused on inherited cardiac diseases in the Netherlands are poor. This situation is unacceptable regarding the potential for prevention of second or more cases in families having suffered from such a dramatic event. Since the two types of interventions, we performed did not improve this suboptimal situation, stricter measures are needed, besides education of the professionals involved. A mandatory assessment of the cause of death in cases of SD in the young should strongly be advised, followed by active referral for cardiogenetic screening of relatives of eligible cases.

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