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Clinical paper

Mutation analysis of cases of sudden unexplained death, 15 years after death: Prompt genetic evaluation after resuscitation can save future lives☆

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ABSTRACT

Introduction: The aim of this study is to use genetic mutation analysis to determine the cause of sudden unexpected death in young (SUDY) persons with normal autopsy findings, and to provide relatives with an identified cardiac mutation with suitable cardiovascular prevention.
Methods: We performed mutation analysis on blood samples from first-degree relatives of 25 cases with normal autopsy findings identified in the national Swedish study of sudden cardiac death in 15- to 35-year-olds from 1992 to 1999.
Results: We found three families with long QT syndrome through mutation screening, and the mutations were verified in two of the deceased. Eight family members were found to be mutation carriers and have been provided with suitable cardiovascular prevention. Mutation screening also identified a number of common polymorphisms in the individuals screened. Clinical history revealed one family each with short QT syndrome and hypertrophic cardiomyopathy, respectively, but no mutations were found in the family members or in the deceased. Two SCDs each had occurred in two of the affected families.
Conclusion: Cardiac/genetic evaluation of relatives long after SUDY can reveal a diagnosis in 5/25 (20%) of cases. Since DNA extraction of formalin fixed paraffin embedded samples is unreliable, it is important that blood or tissue samples be stored at autopsy of such cases. This can facilitate establishing a diagnosis and thereby save lives in the future.

1. Introduction

Sudden cardiac death (SCD) in the young is a rare but tragic event. In several cases it is the first manifestation of disease, rendering its prevention particularly challenging. SCD is defined as a witnessed, natural unexpected death from cardiac causes occurring within 1 h after onset of symptoms in a previously healthy person, or an unwitnessed natural unexpected death of a person observed to be well within 24 h of being found dead.[1] In the general population, SCD is in most cases secondary to coronary artery disease, with an incidence of 1–2 per 1000 patient-years.[2,3] In children and young adults, the SCD incidence is ~1–5 per 100,000 patient-years.[4–7] The young SCD group is heterogeneous with a large spectrum of diagnoses, congenital or acquired, with autopsy findings including coronary artery disease, cardiomyopathies, myocarditis, and coronary artery anomalies. In 10–30% of the cases no structural abnormalities can be detected at autopsy; sudden death is then referred to as autopsy negative or sudden unexplained death (SUD).[8–11] These deaths can be caused by malignant tachyarrhythmias due to inherited primary electrical diseases such as long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT).[12,13] These diseases are caused by mutations in genes encoding cardiac ion channels leading to altered ion-channel activity, and molecular genetic screening can reveal the underlying mutation.[13,14] In a previous study of SCD in the young in Sweden, no diagnosis was established at autopsy in 23% of the cases.[6] In an Australian study, Doolan et al. showed that 31% of young SCD cases were autopsy negative.[15] The diagnosis is important for the mourning process of those left behind, and also gives the opportunity to investigate and offer appropriate treatment to family members.[16]

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Table 1
Characteristics of 25 cases of unexplained sudden cardiac death and genetic assessment of first-degree relatives.

Case no. sex	Age, years	Activity at death	ECG class I = normal II = probably normal III = probably pathological IV = pathological	Premortal symtoms	Family history of SUD	First-degree relatives genetically screened	Identified mutation/(SNP)/disease
1. Female	22	Daily	IV QTc-498 ms	Syncope Dyspnoea	X	Brother	***KCNQ1*/G314S**[a] LQTS[b]
2. Female	32	Sleep	No ECG	Fatigue		Parents	***KCNQ1*/K183M**[a] LQTS (*SCN5A*/H558R[c] *SCN5A*/H558R)[c]
3. Female	17	Sleep	No ECG	Nocturnal dyspnoea Fatigue		Parents	***KCNH2*/R176W**[a] LQTS (*SCN5A*/H558R[c] *KCNH2*/K897T[c] *SCN5A*/H558R[c] *KCNE1*/D85N)[c]
4. Female	27	Sleep	No ECG	Fatigue	X	Mother	SQTS[d]
5. Male	20	Daily	No ECG	No	X	Father	HCM[e]
6. Male	33	Sleep	No ECG	Fatigue	X	Mother	
7. Male	18	Sleep	I	Syncope	X	Mother	0
8. Male	23	Sleep	I	Fatigue Syncope	X	Parents	0
9. Female	19	Daily	No ECG	No		Parents	(*KCNH2*/K897T[c] *SCN5A*/H558R)[c]
10. Male	23	Daily	I	Syncope		Parents	0
11. Male	21	Exercise	III Preexitation	Palpitations		Parents	(*KCNH2*/K897T)[c]
12. Female	35	Daily	No ECG	Fatigue		Mother	(*SCN5A*/H558R)[c]
13. Male	28	Sleep	II	No		Mother	0
14. Male	21	Daily	I	Postinfluenza		Mother	0
15. Male	18	Sleep	No ECG	No		Mother	(*SCN5A*/H558R)[c]
16. Male	21	Sleep	No ECG	No		Parents	(*KCNH2*/K897T[c] *SCN5A*/H558R)[c]
17. Female	31	Daily	II	Palpitations Dizziness		Daughter	0
18. Male	22	Daily	I	No		Parents	0
19. Female	34	Daily	No ECG	No		Mother	0
20. Male	17	Daily	No ECG	Influenza		Parents	(*SCN5A*/H558R)[c]
21. Male	23	Exercise	I	Chest pain		Parents	(*SCN5A*/H558R)[c]
22. Female	24	Daily	No ECG	Dizziness		Parents	0
23. Male	18	Daily	No ECG	No		Father	0
24. Male	17	Daily	No ECG	No		Father	0
25. Male	23	Sleep	III Preexitation	Palpitations		Parents	0

[a] Mutation: *KCNQ1* p.G314S (c.940G>A), *KCNQ1* p.K183M (c.548A>T), *KCNH2* p.R176W (c.526C>T).
[b] LQTS = long QT syndrome.
[c] SNP: *KCNE1*/D85N, (rs1805128), *KCNH2*/K897T, (rs1805123), *SCN5A*/H558R, (rs1805124).
[d] SQTS = short QT syndrome.
[e] HCM = hypertrophic cardiomyopathy.

2. Methods

2.1. Inclusion of index cases

In the following, deceased individuals are denoted as "cases" and surviving first-degree relatives as "subjects". Among 181 cases in the national Swedish study, 15–35 years of age, deceased from SCD during 1992–1999, 40 (23%) cases with normal findings at forensic autopsy were identified.[6] We aimed to include these 40 cases, but five were excluded because their relatives had declined participation in a former interview study, and four additional cases were excluded as no autopsy tissue was found. For each of the remaining 31 cases, a first-degree relative or spouse was contacted, by telephone and by letter. In six cases, contact could not be established. Thus, 25 cases of SUD were ultimately included in the study. From these 25 cases we identified 37 first-degree relatives (Table 1) for additional testing. Tissue blocks from the deceased cases were assembled from the six forensic departments in Sweden. Data on index cases were collected from forensic autopsy reports, police reports and interviews with family members. ECGs were available in 11/25 cases (44%), previously coded according to the Minnesota Code criteria (Table 1).[17]

2.2. Genetic analysis

We collected blood samples from 37 first-degree relatives and performed mutation screening of DNA. Screening of the LQTS-genes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*) was performed in all subjects: 34 of 37 were screened for mutations in the *RYR2* gene (CPVT), one parent was additionally screened for the *KCNJ2* gene (SQTS), and one parent with hypertrophic cardiomyopathy (HCM) was screened for mutations in the *MYBPC3* and *MYH7* genes. In deceased cases, DNA was extracted from formalin fixed paraffin embedded tissue (FFPE), and a search for mutations identified in first-degree relatives was performed.

2.3. Methods of genetic analysis

Coding exons of the *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *MYBPC3* and *MYH7* genes and adjacent intronic sequences