Psychological adaptation to molecular autopsy findings following sudden cardiac death in the young

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Purpose: Sudden cardiac death (SCD) in the young is a devastating event occurring in otherwise healthy individuals. Postmortem genetic testing (molecular autopsy) may help identify a cause, though there is potential for uncertainty. We report psychological adaptation to molecular autopsy findings amongst family members after a young SCD.

Methods: First-degree relatives who had experienced a SCD of a young relative and attended a specialized cardiac genetic clinic were invited to complete a cross-sectional, self-report survey comprising a number of validated scales. Clinical, genetic, and family history information was collected from the medical record.

Results: Thirty-three individuals from 27 families (response rate 48%) completed a survey (mean age 49 ± 12 years, 49% were mothers of the decedent). Eleven (36%) reported poor adaptation to genetic information, and compared with those with good adaptation, they were more likely to have worse posttraumatic stress

symptoms ($p = 0.0004$) and depression ($p = 0.01$). Perceived support was lower in those reporting poor adaptation, including social support ($p < 0.0001$) and perceived support from significant others ($p = 0.03$), family members ($p = 0.001$), and friends ($p = 0.0002$).

Conclusion: Adaptation to molecular autopsy findings may be difficult for some relatives following a young SCD. Careful pretest genetic counseling and integration of psychological support is needed.

Genetics in Medicine (2019) 21:1452–1456; <https://doi.org/10.1038/s41436-018-0338-4>

Keywords: sudden cardiac death; molecular autopsy; genetic testing; psychological adaptation

INTRODUCTION

Sudden cardiac death (SCD) in the young is a tragic event. The annual incidence of SCD in the young is 1.3 cases per 100,000 persons, and 40% will have no cause of death identified at postmortem examination.¹ Inherited heart diseases account for the large majority of SCD under the age of 35 years. Structural causes such as inherited cardiomyopathies are often evident at postmortem, while primary arrhythmia disorders account for a proportion of the unexplained deaths.² In most cases these diseases are autosomal dominantly inherited, and first-degree relatives have a 1 in 2 risk of disease. Ascertaining a cause of death therefore not only gives closure to the family, but also can help to inform clinical surveillance of the family. The molecular autopsy is increasingly recognized as an important aspect in SCD investigation.² Clinically relevant variants may be identified in 10–15% of cases;^{1,3} however, most families

will receive an indeterminate (no causative variants identified) or uncertain result (variants of uncertain significance; VUS).

This uncertainty can pose a challenge, especially in the setting of SCD where there is known to be a high rate of poor psychological functioning in relatives. In patients with hypertrophic cardiomyopathy, uncertainty can impact on psychological adjustment, understanding, and subsequent family communication.⁴ Many SCD events occur with no warning signs, leaving the family with many questions regarding risk to themselves and family members. How a grieving family will comprehend and adapt to the inherent uncertainty and complexity of genetic information from postmortem genetic testing is largely unknown. Here we explore psychological adaptation to the molecular autopsy findings and the factors associated with worse outcomes amongst family members following the SCD of a young, previously healthy relative.

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Submitted 17 July 2018; accepted: 3 October 2018

Published online: 16 October 2018

MATERIALS AND METHODS

Participants and recruitment

Family members attending a specialized multidisciplinary genetic heart disease clinic in Sydney, Australia who had experienced the SCD of a young relative (aged 1–40 years) where an inherited heart disease was either diagnosed or suspected were invited to participate. Inclusion criteria were adult (≥ 18 years) first-degree relatives, where there was no premorbid diagnosis of an inherited heart disease in the proband or family, and postmortem genetic testing had been performed. Local institutional Human Research Ethics Committee approval was granted and all participants gave written informed consent. The specialized clinic includes cardiologists and genetic counselors, with external links to clinical psychological support as needed.

Clinical and genetic data

All eligible families had been seen in our specialized multidisciplinary clinic and detailed information was sought from the medical record. A cardiac genetic counselor collected the family history information. Details of the decedent were collected from the postmortem report. Genetic test results were reviewed according to American College of Medical Genetics and Genomics and Association Association for Molecular Pathology (ACMG/AMP) criteria,⁵ and are shown as the classification at the time of survey completion. Outcomes of family screening and new family diagnoses were recorded.

Psychosocial survey scales

The cross-sectional, self-report survey was comprised of the Psychological Adaptation to Genetic Information Scale (PAGIS),⁶ Impact of Events Scale—Revised (IES-R),⁷ Hospital Anxiety and Depression Scale (HADS),⁸ and the Multidimensional Scale of Perceived Social Support (MSPSS).⁹

PAGIS is a validated instrument designed to measure a person's response to and coping with complex genetic information.⁶ It is a 26-item, six-point Likert scale informing five subdomains: nonintrusiveness (freedom from uncontrolled thoughts and feelings about the genetic risk), support (relationships with others that allow discussion regarding the genetic risk), self-worth (impact of knowledge of genetic risk on self-esteem), certainty (perception of accurate knowledge of the genetic risk), and self-efficacy (perception of control over the consequences of the genetic risk). The HADS is a validated scale used extensively in hospital settings and measures clinically relevant anxiety (HADS-Anxiety) and depression (HADS-Depression).⁸ The IES-R is a validated scale used widely to identify posttraumatic stress symptoms,⁷ while the MSPSS is a validated scale used to measure subjective social support from friends, family, and significant others.⁹

Statistical analysis

A binary score for the PAGIS scale was created and used as the primary outcome of interest, with patients grouped into

those who are/are not psychologically adapted to the genetic information obtained from the molecular autopsy. A PAGIS cutoff score of 96 was chosen, based on the participant reporting a negative response to the majority of scale statements (PAGIS score < 96 indicates poorer adaptation). Data were analyzed using GraphPad Prism version 7. Continuous variables were analyzed using unpaired *t*-tests and analysis of variance (ANOVA), while categorical variables were analyzed using Fisher's exact tests. Data are shown as mean $\pm$ standard deviation or *n* (%) for continuous and categorical variables, respectively. A *p* value of < 0.05 was considered statistically significant.

RESULTS

Population characteristics

There were 75 eligible participants; 6 were unable to be contacted and 33 surveys were returned (response rate 48%) from 27 families. The mean age of the participants was 49 ± 12 years (range: 21–66 years), with 8 (24%) being male and 13 (39%) having a university education. Sixteen (48%) participants were mothers of the decedent. There were 4 (12%) participants who witnessed the death. There were 8 participants who had a clinical diagnosis of disease subsequent to the death, and of those 7 also carried the causative variant in the family.

Decedent and genetic testing characteristics

Amongst decedents (*n* = 27), the mean age of death was 22 ± 10 years (range: 0.2–39 years) and 19 (70%) were male. The mean time since death was 8 ± 6 years (range: 2–31 years) and a cause of death at postmortem examination was made in 14 (52%) cases. Molecular autopsy findings included 7 (26%) likely pathogenic/pathogenic variant results, 12 (44%) uncertain, and 8 (30%) indeterminate results (Table 1). Genetic testing performed varied widely due to the evolution of the process in recent years, and the gene panel size ranged from 5 to 170 genes.

Psychological adaptation to genetic information

There were 11 of 31 (36%) participants who reported poor adaptation to the genetic information obtained from the molecular autopsy (PAGIS score < 96 ; Table 2). Relatives with poor adaptation had a mean age of 49 ± 11 ; 3 (27%) were male and 5 (45%) were mothers of the decedent. They reported significantly worse psychological wellbeing, including post-traumatic stress symptoms (mean IES-R; 17 ± 15 vs. 43 ± 20 , *p* = 0.0004) and HADS depression (3.6 ± 3.6 vs. 7.6 ± 4.7 , *p* = 0.01).

Perceived support was lower in those reporting poor adaptation, including social support (4.7 ± 0.5 vs. 6.0 ± 0.7 , *p* < 0.0001) and perceived support from significant others (5.5 ± 1.0 vs. 6.2 ± 0.7 , *p* = 0.03), family members (4.6 ± 1.1 vs. 6.0 ± 0.9 , *p* = 0.001), and friends (4.4 ± 1.0 vs. 5.8 ± 0.8 , *p* = 0.0002). Fewer participants reported being satisfied with medical and psychosocial support received compared with those with better adaptation (17 [94%] vs. 6 [54%], *p* = 0.02),

Table 1 Molecular autopsy genetic results

Family code	Age at death, years	Gender of deceased	COD at PM	Positive family hx since death	Genetic testing result	Gene	Variant	Panel / Genes included
ADZ	23	Male	Undetermined	Yes	VUS	<i>TMPO</i>	p.Pro426Leu	SCD / 69
AUR	1	Male	Undetermined	No	Indet	—	—	SCD / 69
WH	24	Male	Undetermined	No	LP	<i>SCN5A</i>	p.Gly1642Glu	SCD / 101
ATL	24	Female	Undetermined	No	Indet	—	—	SCD / 69
ALB	25	Female	Undetermined	Yes	Path	<i>ACTN2</i>	p.Ala119Thr	SCD / 94
AVT	20	Male	Undetermined	No	VUS	<i>CACNB2</i>	p.Ala72Val	SCD / 94
QW	30	Male	Undetermined	Yes	LP ^a	<i>KCNQ1</i>	p.Val129Gly	LQTS / 5
AKU	26	Male	ARVC	Yes	Indet	—	—	ARVC / 7
QF	17	Male	Yes	Yes	Path	<i>PKP2</i>	p.A733fsX740	ARVC / 4
AXK	8	Male	Undetermined	No	VUS	<i>TRPM4</i>	p.Ile335Thr	SCD / 94
AQR	21	Female	Undetermined	No	VUS	<i>MYH6 / HCN4</i>	p.Val496Leu / p. Glu1193Gln	SCD / 69
NR	21	Male	Undetermined	No	VUS	<i>KCNH2</i>	p.Gly487Ser	LQTS / 5
RH	23	Male	Undetermined/ Drowning	No	Indet	—	—	LQTS / 5
APS	24	Male	Undetermined	No	VUS	<i>AKAP9</i>	p.Arg3750His	SCD / 69
AWW	2	Male	Undetermined	No	Indet	—	—	SCD / 69
AQI	31	Male	Undetermined	No	Indet	—	—	SCD / 97
BAL	28	Female	HCM	Yes	LP	<i>MYBPC3</i>	p.Gly853Alafs*26	—
AAN	32	Female	Probable postviral cardiomyopathy	Yes	VUS	<i>DSP / TNNI3</i>	p.Arg160X / p. Ser166Pro	SCD / 170
WJ	34	Male	HCM	Yes	VUS	<i>MYH7</i>	p. Arg1818Trp / p. Asp778Val	SCD / 65
MG	16	Male	Possible HCM	No	Indet	—	—	SCD / 46
IH	10	Male	Undetermined	Yes	Path	<i>KCNH2</i>	p.Ala913Val	LQTS / 5
AWC	9 wks	Female	LVNC/LQTS	No	VUS	<i>TTN / DSP</i>	p.Ala26198Va; p. Ala26198Ser / c.*9T>A	SCD / 97
ATR	27	Male	Undetermined	No	VUS	<i>LDB3</i>	p.Val313Ile	SCD / 97
BFQ	40	Female	Undetermined	No	VUS	<i>RMB20 / CBS / TGFB2</i>	p.Phe1062Ser / p. Arg369Cys / p. Val217Ile	SCD / 100
AAF	39	Male	ARVC	Yes	Indet	—	—	SCD / 174
TD	21	Male	HCM	Yes	VUS	<i>ANK2</i>	p.G3733del	SCD / 128
RJ	21	Female	Undetermined	Yes	LP ^a	<i>KCNQ1</i>	p.Arg397Gln	LQTS / 5

Classifications shown are current at the time of participant survey completion.

ARVC arrhythmogenic right ventricular cardiomyopathy, COD cause of death, HCM hypertrophic cardiomyopathy, hx history, Indet indeterminate, LP likely pathogenic, LQTS long QT syndrome, LVNC left ventricular noncompaction, Path pathogenic, PM postmortem, SCD sudden cardiac death, VUS variant of uncertain significance, wks weeks.

^aIndicates a gene result that has since been downgraded to VUS.

and they were more likely to have issues with communication of the genetic information to their family (64% vs. 22%, $p = 0.048$). They also were more likely to have a negative or neutral perception (8 [73%] vs. 2 [11%], $p = 0.001$) of the genetic testing process.

The least endorsed items of the PAGIS were “I rarely think about the fact that I have the genetic risk” (3.7 of 6; nonintrusiveness), “I am confident that I can work out any problems having the genetic risk might cause” (3.8 of 6; self-efficacy), and “I believe there are things I can do to avoid the problems that may arise from having the genetic risk” (scored 3.8 of 6; self-efficacy).

DISCUSSION

This study sought to evaluate first-degree family members' psychological adaptation to genetic information obtained from molecular autopsy after the sudden cardiac death of a young relative. One third of the first-degree relatives had poor psychological adaptation and were more likely to report worse posttraumatic stress and depressive symptoms; poor perceived familial, social, and medical support; issues communicating information to the family; and had a negative view of the molecular autopsy process. Given the cross-sectional study design it is not possible to ascertain cause and effect; however a reasonable hypothesis would be that overall poor

Table 2 Clinical and psychosocial characteristics of participants based on adjustment to genetic information

	Good adaptation	Poor adaptation	<i>p</i> value
Clinical and psychosocial characteristics			
Number of participants ^a	20 (65)	11 (35)	-
Male sex	5 (25)	3 (27)	0.99
Clinically affected	6 (30)	2 (18)	0.68
Mother of decedent	9 (45)	5 (45)	0.99
Death witnessed	1 (5)	2 (18)	0.28
Characteristics of decedent			
Age at death, years	21 ± 10	24 ± 10	0.38
COD at PM	11 (55)	3 (27)	0.26
Time since death, years	9 ± 6	7 ± 5	0.26
Postmortem genetic testing			
Indeterminate	6 (30)	2 (18)	0.15
Uncertain	10 (50)	9 (82)	
Pathogenic/likely pathogenic	4 (20)	0 (0)	
Time between death & result, months	52 ± 54	46 ± 58	0.79
Time since result, months	58 ± 29	39 ± 12	0.05
Impact of Events Scale			
Posttraumatic stress, mean score	17 ± 15	43 ± 20	0.0004
Hospital Anxiety and Depression Scale			
HADS-Anxiety, mean score	5.8 ± 4.0	8.5 ± 4.2	0.09
HADS-Depression, mean score	3.6 ± 3.6	7.6 ± 4.7	0.01
Medical and social support			
Total MSPSS support score	6.0 ± 0.7	4.7 ± 0.5	<0.0001
Significant other support score	6.2 ± 0.7	5.5 ± 1.0	0.03
Family support score	6.0 ± 0.9	4.6 ± 1.1	0.001
Friend support score	5.8 ± 0.8	4.4 ± 1.0	0.0002
Satisfaction with support	17 (94)	6 (54)	0.02
Needed more support	8 (50)	4 (36)	0.4
External support sought	11 (65)	7 (64)	0.99
Communication of result to family			
No issues	14 (78)	4 (36)	0.048
Some issues	4 (22)	7 (64)	
Overall impact of genetic testing			
Positive impact	16 (89)	3 (27)	0.03
Negative impact	0 (0)	2 (18)	
Neutral impact	2 (11)	6 (55)	

Data shown as mean ± standard deviation or *n* (%).

COD cause of death, HADS Hospital Anxiety and Depression Scale, MSPSS Multi-dimensional Scale of Perceived Support, PAGIS Psychological Adaptation to Genetic Information Score, PM postmortem.

^aTwo participants did not complete the PAGIS scale questions in its entirety.

psychological adjustment after the death likely influences all aspects of coping, including adaptation to the genetic information arising from the molecular autopsy. Strategies to better identify and support those with poor psychological

adaptation to a molecular autopsy result need to be considered and support the need for a clinical psychologist to have a role within existing specialist genetic heart disease multidisciplinary clinics.

Our previous research has identified the unique psychosocial and clinical needs of this population. Psychologically, family members are at an increased risk of anxiety, prolonged grief, and posttraumatic stress, with at least 1 in 2 family members reporting clinically significant symptoms on average 6 years after the SCD of their young relative.^{10,11} Indeed, we found 53% of participants in this current study had posttraumatic stress symptoms above the clinically significant cutoff of 24 (26 ± 21) after a mean time of 8 ± 6 years. There are significant and long-term emotional implications for the family, but particularly for those who witnessed the death.¹⁰ Previous research to understand the situational factors affecting bereavement further signify this population's high risk of adverse grief reactions due to the potential perception of responsibility, blame, and guilt from the inherited nature of the condition¹² and potential for unanswered questions regarding cause of death.

We believe this is the first study to look at first-degree relatives' psychological adaptation to the genetic information obtained at postmortem through a molecular autopsy. According to Biesecker and Erby, adaptation refers to "both the process of coming to terms with the implications of the condition or risk, and the observable outcomes of that process."¹³ The concepts of adaptation are complex and multidimensional, impacted by cognitive, affective, behavioral, and interpersonal factors, as represented by the five subscales of the PAGIS scale: self-efficacy, support, nonintrusiveness, self-worth, and certainty.⁶ We found one third of relatives had poor psychological adaptation to the genetic information received (PAGIS <96). Existing studies focused on adaptation to a genetic condition or risk and largely relate to parental adaptation to rare syndromes, and identified that while the majority adapt well, those with difficulty can benefit from intervention.¹⁴ The factors associated with adaptation would therefore be salient to identify in future research to direct psychological management of family members.

Existing research has shown that the genetic testing itself is not associated with stress beyond that of clinical testing.^{14,15} Qualitative research to understand a family's motivation for pursuing genetic testing after SCD has shown that parents overwhelmingly and understandably seek answers in an attempt to make sense of why their child died, and to prevent another SCD from happening in their family.¹¹ This attempt to make sense of the loss of a young person has been reported as a salient predictor of postloss adjustment, with meaning-making contributing to the intensity of complicated grief symptoms.¹⁶ This may be particularly relevant to the context of molecular autopsy findings, where failing to find meaning could further interfere with grieving.¹⁷ While there was no statistically significant association, we observed that 82% of family members who reported poor adaptation received a VUS result, compared with 50% in the better-adapted group.

Adaptation is a multidimensional process and may require additional psychological support.¹⁸ One area that has so far not been widely investigated in this setting is greater support in feeding back the gene result through the use of a communication aid, and potentially highlights a high-impact role of cardiac genetic counselors.^{19,20}

Limitations of the study include a modest sample size, though we were able to demonstrate statistical power for large effects. Caution should be taken in interpreting subanalyses where the sample size is small. Potential bias may have been introduced due to the more recent shift to comprehensive panel testing, which has a greater chance of producing uncertain results, and this could not be controlled for. In addition, there was a wide interval between the time since death for participants. The majority of respondents were mothers of the decedents and this is primarily due to the mother being our main contact to the family. Use of the PAGIS as a binary score should be examined in a larger patient population. It should additionally be noted that all participants in this setting were seen in a specialized cardiac genetics clinic with multidisciplinary care,² and adaptation to molecular autopsy genetic testing results may therefore be overestimated in this setting.

Our study represents the first investigation into psychological adaptation to molecular autopsy findings after the SCD of a young relative. With significant efforts of research groups worldwide to elucidate the underlying genetics of sudden cardiac death in the young, appreciation of the potential psychosocial implications is crucial. We further emphasize the need for clinical psychological support to be integrated into the specialized multidisciplinary genetic heart disease clinic.

ACKNOWLEDGEMENTS

J.S. is the recipient of the Elizabeth and Henry-Hamilton Browne Scholarship from the University of Sydney. C.S. is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (1059156). J.I. is the recipient of a National Heart Foundation of Australia Future Leader Fellowship (100833). This study is funded in part by an NHMRC Project Grant (1059515).

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374:2441–2452.
2. Semsarian C, Ingles J, Wilde AA. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. *Eur Heart J*. 2015;36:1290–1296.
3. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. *J Am Coll Cardiol*. 2017;69:2134–2145.
4. Burns C, Yeates L, Spinks C, Semsarian C, Ingles J. Attitudes, knowledge and consequences of uncertain genetic findings in hypertrophic cardiomyopathy. *Eur J Hum Genet*. 2017;25:809–815.
5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424.
6. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;37:203–208.
7. Weiss D, Marmar C. The impact of event scale—revised. New York: The Guilford Press; 1997.
8. Zigmond A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–370.
9. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the Multidimensional Scale of Perceived Social Support. *J Pers Assess*. 1990;55:610–617.
10. Ingles J, Spinks C, Yeates L, McGeechan K, Kasparian N, Semsarian C. Posttraumatic stress and prolonged grief after the sudden cardiac death of a young relative. *JAMA Intern Med*. 2016;176:402–405.
11. Yeates L, Hunt L, Saleh M, Semsarian C, Ingles J. Poor psychological wellbeing particularly in mothers following sudden cardiac death in the young. *Eur J Cardiovasc Nurs*. 2013;12:484–491.
12. Brent D, Melhem N, Donohoe MB, Walker M. The incidence and course of depression in bereaved youth 21 months after the loss of a parent to suicide, accident, or sudden natural death. *Am J Psychiatry*. 2009;166:786–794.
13. Biesecker BB, Erby L. Adaptation to living with a genetic condition or risk: a mini-review. *Clin Genet*. 2008;74:401–407.
14. Rhodes A, Rosman L, Cahill J, et al. Minding the genes: a multidisciplinary approach towards genetic assessment of cardiovascular disease. *J Genet Couns*. 2017;26:224–231.
15. Ingles J, Yeates L, O'Brien L, et al. Genetic testing for inherited heart diseases: longitudinal impact on health-related quality of life. *Genet Med*. 2012;10:117–20.
16. Keesee NJ, Currier JM, Neimeyer RA. Predictors of grief following the death of one's child: the contribution of finding meaning. *J Clin Psychol*. 2008;64:1145–1163.
17. Erskine KE, Hidayatallah NZ, Walsh CA, et al. Motivation to pursue genetic testing in individuals with a personal or family history of cardiac events or sudden cardiac death. *J Genet Couns*. 2014;23:849–859.
18. Heiniger L, Price MA, Charles M, Butow PN, kConFab Psychosocial Group on behalf of the kConFab Investigators. Facilitators and challenges in psychosocial adaptation to being at increased familial risk of breast cancer. *J Genet Couns*. 2015;24:890–907.
19. Burns C, James C, Ingles J, GradDipGenCouns JI. Communication of genetic information to families with inherited rhythm disorders. *Heart Rhythm*. 2017;15:780–786.
20. Smagarinsky Y, Burns C, Spinks C, Semsarian C, Ingles J. Development of a communication aid for explaining hypertrophic cardiomyopathy genetic test results. *Pilot Feasibility Stud*. 2017;3:53.