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Pedro Filipe Amorim Machado

Sudden Infant Death Syndrome
Síndrome da Morte Súbita do Lactente

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Pedro Filipe Amorim Machado

Sudden Infant Death Syndrome

Síndrome da Morte Súbita do Lactente

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NOME

Pedro Filipe Amorim Machado

NÚMERO DE ESTUDANTE	E-MAIL
201200148	pedro.filipe.amorim.machado@gmail.com

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Sudden Infant Death Syndrome

ORIENTADOR

Prof. Doutor Manuel Joaquim Lopes Vaz Da Silva

COORIENTADOR (se aplicável)

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DEDICATÓRIA

Esta dissertação não representa apenas o resultado de extensas horas de estudo, reflexão e trabalho durante as diversas etapas que o constituem. É igualmente o culminar de um objetivo académico a que me propus e que não seria possível sem a ajuda de um número considerável de pessoas. Tantas que jamais seria possível referi-las a todas neste espaço a elas dedicado.

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À Dani... Mais uma tese, mais um agradecimento... Os anos passam e a amizade perdura... Como é que ainda nos conseguimos aturamos... É um mistério da vida... Mas daqueles que não vale a pena desvendar... Porque não haja dúvidas, as nossas vidas estarão ligadas até ao dia em que a Segurança Social ou a Polícia nos separe!

Para a minha paixão, deixo uma frase especial que traduz mais do que alguma vez conseguiria dizer neste curto espaço... "There's not enough words..."

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Index

ABSTRACT

Sudden death (SD) is a term used to describe an unexpected and non-traumatic fatal event that occurred within 1 hour of the onset of new or worsening symptoms in an apparently healthy individual or, if unwitnessed, within 24 hours of last being seen in good health. If the SD of an infant aged below 1 year of age cannot be explained, even after a thorough investigation (which includes post-mortem examination, death scene investigation and review of the clinical history), then it is referred as sudden infant death syndrome (SIDS).

SIDS is one of the leading causes of post-neonatal infant mortality in developed countries. The definitive mechanisms are still uncertain and, as such, SIDS remains a diagnosis of exclusion.

Mutations in genes linked to inherited arrhythmia syndromes (e,g channelopathies causing electric disorders) and cardiomyopathies (structural heart abnormalities related to mutations in genes encoding various types of proteins, such as, sarcomeres, desmosomes, the cytoskeleton and the nuclear envelope) have been proposed as the substrate for an infant's underlying vulnerability.

In this review, we will summarize the most recent clinical and molecular observations regarding two of the most common channelopathies associated with SIDS, long QT syndrome (LQTS) and Brugada syndrome (BrS), and one of the most common cardiomyopathy linked to sudden death in the young, hypertrophic cardiomyopathy (HCM). The implications of genetic testing in SIDS cases and subsequent clinical and genetic testing in family members will also be discussed.

Keywords: *Sudden Infant Death Syndrome; Inherited Arrhythmia Syndromes; Long QT Syndrome; Brugada Syndrome; Structural Heart Abnormalities; Hypertrophic Cardiomyopathy; Molecular Autopsy*

RESUMO

Morte súbita (MS) é um termo que descreve um evento fatal súbito e não-traumático que ocorre na primeira hora após o início ou o agravamento de sintomas em indivíduos aparentemente saudáveis ou, caso não seja testemunhado, dentro de 24 horas depois do indivíduo ter sido visto em boa saúde. Se a MS envolver um lactente com idade inferior a 1 ano e não for possível obter uma explicação para este evento, mesmo após uma investigação exaustiva (que inclui exame post mortem, investigação do local da morte e revisão da história clínica), então referimo-nos a este evento como síndrome da morte súbita do lactente (SMSL).

A SMSL é uma das principais causas de mortalidade infantil neonatal nos países desenvolvidos. Os mecanismos definitivos que levam a este evento ainda não estão completamente esclarecidos e, como tal, a SMSL permanece um diagnóstico de exclusão.

As mutações em genes associados a síndromes arritmogénicas hereditárias (por exemplo, canalopatias que causam alterações no sistema de condução eléctrico) e a cardiomiopatias (doenças estruturais cardíacas desencadeadas por mutações em genes que codificam vários tipos de proteínas, como, por exemplo, sarcómeros, desmossomas, o citoesqueleto e a membrana nuclear) foram propostas como sendo o substrato para a vulnerabilidade intrínseca dos lactentes vítimas de SMSL.

Nesta revisão iremos sumariar as mais recentes observações clínicas e moleculares acerca de duas das canalopatias mais associadas à SMSL, a síndrome do QT longo e a síndrome de Brugada, bem como uma das cardiomiopatias mais frequente ligadas à morte súbita nos jovens, a cardiomiopatia hipertrófica. As implicações de testes genéticos nos casos de SMSL e os testes clínicos e genéticos realizados subsequentemente aos membros familiares serão também alvo de discussão.

Palavras-chave: *Síndrome de Morte Súbita do Lactente; Síndromes Arritmogénicas Hereditárias; Síndrome do QT Longo; Síndrome de Brugada; Doenças Estruturais Cardíacas; Cardiomiopatia Hipertrófica; Autópsia Molecular*

LIST OF ABBREVIATIONS

BrP – Brugada Pattern

BrS – Brugada Syndrome

CMR – Cardiac Magnetic Resonance

CT – Computed Tomography

ECG – Electrocardiogram

EHRA – European Heart Rhythm Association

ESC – European Society of Cardiology

ICD – Implantable Cardioverter Defibrillator

HCM – Hypertrophic cardiomyopathy

HRS – Heart Rhythm Society

LQTS – Long QT Syndrome

NGS – Next Generation Sequencing

QTc – QT interval corrected for heart rate

SCD – Sudden Cardiac Death

SD – Sudden Death

SIDS – Sudden Infant Death Syndrome

SUID – Sudden Unexpected Infant Death

US – United States

VF – Ventricular Fibrillation

VT – Ventricular Tachycardia

WES – Whole-Exome Sequencing

SUDDEN CARDIAC DEATH

Sudden death (SD) is a term used to describe an unexpected and non-traumatic fatal event that occurred within 1 hour of the onset of new or worsening symptoms in an apparently healthy individual or, if unwitnessed, within 24 hours of last being seen in good health. When SD involves infants below 1 year of age, and an autopsy has not been performed, it's referred as sudden unexpected infant death (SUID) [1].

Identifying the settings that might have led to the unexpected death of an individual not only provides the family with some understanding but might also allow to perceive if the risk of SD extends to family members. As such, it stands to reason that all unexplained SD victims should undertake an autopsy to investigate the causes that might have led to the unexpected death. If the SD of an infant aged below 1 year of age cannot be explained, even after a thorough investigation (which includes post-mortem examination-autopsy, death scene investigation and review of the clinical history and social history), then it is referred as sudden infant death syndrome (SIDS) [1].

Even though there have been advances in the understanding of the pathophysiology of SIDS, the definitive mechanisms are still uncertain and, as such, it remains a diagnosis of exclusion [2]. Several mechanisms have already been proposed to try to elucidate the mechanisms by which SIDS occurs, such as metabolic disorders and morphological changes in the brainstem, which may be the cause of respiratory dysfunction and cardiorespiratory instability due to immaturity of centers responsible for these functions [3].

More recently, there has been an increasing consciousness that cardiac hereditable syndromes, which includes cardiomyopathies and channelopathies, may be greatly associated with SIDS [4]. Infants with inherited arrhythmia syndromes could die from sudden cardiac arrest due to ventricular tachycardia and/or ventricular fibrillation. Normal autopsy procedures cannot detect these changes, since the heart is structurally normal. This would be the opposite of cardiomyopathies, where normal autopsy procedures are able to detect signs of disease. However it has been hypothesized that in some cardiomyopathies there may be a concealed arrhythmogenic phase before the

manifestation of structural defects, which wouldn't be detected during the normal autopsy procedures [5, 6].

In this review, we will summarize the most recent clinical and molecular observations regarding two of the most common channelopathies associated with SIDS, long QT syndrome (LQTS) and Brugada syndrome (BrS), and one of the most common cardiomyopathy linked to sudden death in the young, hypertrophic cardiomyopathy (HCM).

METHODS

The PubMed database was used to perform this review of the literature. using the key words "sudden infant death syndrome" with a date of publication between January of 2007 and December of 2017. After reading the abstracts the articles deemed relevant for this work were selected. Furthermore, the list of references of these articles were also analyzed.

EPIDEMIOLOGY AND RISK FACTORS

In 2013, the United States (US) reported 3,422 deaths categorized as SUIDs, which comprised around 14,6% of total infant deaths. These included deaths from SIDS, asphyxiation during sleep and deaths in which there was insufficient information to categorize the cause. About 2,300 of these deaths were attributable to SIDS [7].

The greatest hallmark in the reduction of SIDS rates happened in the 1980s thanks to the discovery that the prone sleep position triples the likelihood of SIDS. This led to the implementation of public health campaigns entitled "Back to Sleep", promoting a supine sleep position for infants. Studies carried out after the implementation of this campaign have shown that rates of prone sleep position decreased to 2-5% with a reduction of SIDS rates by 50-90% [8, 9]. Given the strength of this single factor in the decline of SIDS rates, the American Academy of Pediatrics is still promoting these recommendations (Table 1) [10].

Table 1 – Summary of recommendations developed to reduce the risk of SIDS by strength of recommendation. (taken from [10])

A-level recommendations
Back to sleep for every sleep
Use a firm sleep surface
Breastfeeding is recommended
Room-sharing with the infant on a separate sleep surface is recommended
Keep soft objects and loose bedding away from the infant's sleep area
Consider offering a pacifier at naptime and bedtime
Avoid smoke exposure during pregnancy and after birth.
Avoid alcohol and illicit drug use during pregnancy and after birth
Avoid overheating
Pregnant women should seek and obtain regular pre-natal care
Infants should be immunized in accordance with AAP and CDC recommendations
Do not use home cardiorespiratory monitors as a strategy to reduce the risk of SIDS
Health care providers, staff in newborn nurseries and NICUs, and child care providers should endorse and model the SIDS risk-reduction recommendations from birth
Media and manufacturers should follow safe sleep guidelines in their messaging and advertising
Continue the "Safe to Sleep" campaign, focusing on ways to reduce the risk of all sleep-related infant deaths, including SIDS, suffocation, and other unintentional deaths. Pediatricians and other primary care providers should actively participate in this campaign
B-level recommendations
Avoid the use of commercial devices that are inconsistent with safe sleep recommendations
Supervised, awake tummy time is recommended to facilitate development and to minimize development of positional plagiocephaly
C-level recommendations
Continue research and surveillance on the risk factors, causes, and pathophysiologic mechanisms of SIDS and other sleep-related infant deaths, with the ultimate goal of eliminating these deaths entirely
There is no evidence to recommend swaddling as a strategy to reduce the risk of SIDS

However, despite the significant decrease in the last decades, SIDS rates have remained stable since 2001, being one of the leading causes of post-neonatal infant death in developed countries (Figure 1) [11].

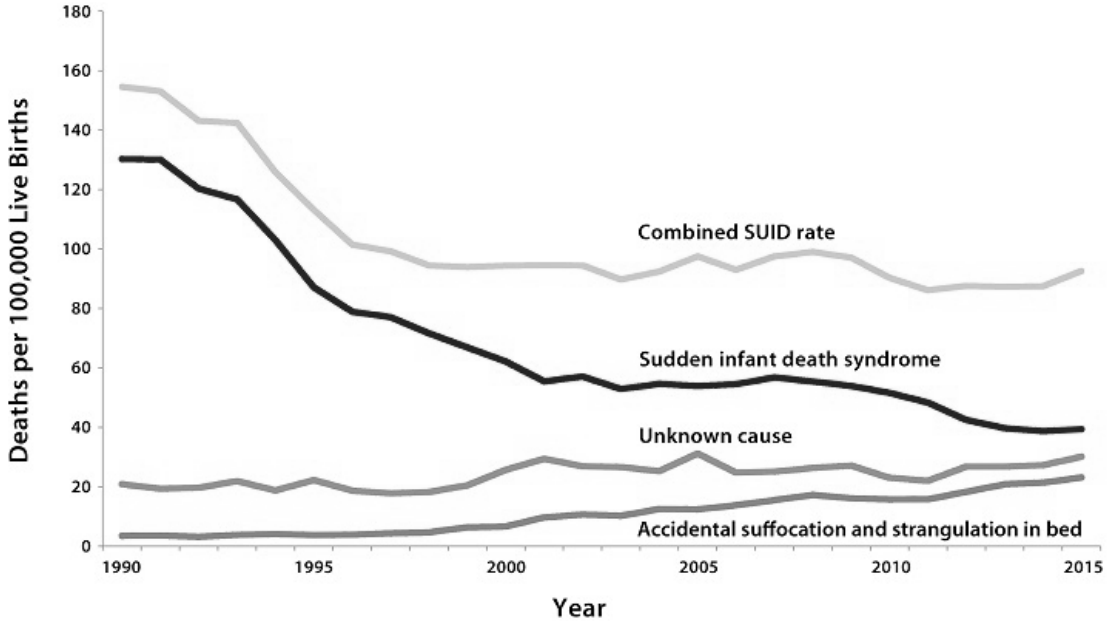

Figure 1 – Trends in sudden unexpected infant death by cause from 1990 to 2015. (taken from [11])

A multitude of risk factors for SIDS have already been identified (Table 2), such as environmental factors, maternal factors and neonatal factors (including genetic factors). Social inequalities remain a key factor in the epidemiology of SIDS since it occurs increasingly in situations of social deprivation. Racial and ethnic disparities in SIDS are also pronounced, which might reflect these socioeconomic inequalities. In the US, American Indian and non-Hispanic black infants were two times more likely to die from SIDS. Moreover, pre-natal and post-natal exposure to smoking, bed sharing, prone sleeping position and male gender also remain to be a significant risk (Table 2) [7, 12–14].

Table 2 – Etiology/risk factors of SIDS. (taken and adapted from [3, 13])

Biological
Prematurity and low birth weight
1:5 infants who died from SIDS were premature. Low birth weight has been linked to a delayed maturation regarding the ability to move the head from the face down position to face up position
Apnea
2-4% of infants who die from SIDS have a history of apnea which may be caused by regurgitation of gastric content that has an acidic pH, which leads to hypoxia
Infection
Gastroenteritis, otitis media and upper respiratory tract infection have been the major infectious conditions found at the time of death in infants. Particularly, the respiratory syncytial virus has been shown to cause episodes of apnea in children, which leads to hypoxia and possibly death
Gender (males)
Male infants who died from SIDS have been found to have a higher apoptosis rate in the brainstem which can lead to absence of touch and proprioception, limiting an infant when he tries to adopt a supine position from a prone position
Familial
Infants that are not breastfed
Maternal age and education
Mothers of infants who died from SIDS are more likely to be young
Maternal smoking, maternal and paternal recreational drug usage
Decreased lung capacity and changes in the arousal mechanism of infants have been linked to pre-natal exposure to nicotine. Other drugs, particularly cocaine, have also been implicated in SIDS rates, by causing maturational delay and respiratory instability
Maternal history of hospitalization for psychiatric illness
SIDS has been linked to mothers who have a history of depression, particularly with a diagnosis in the year previous to the birth or post-neonatal
Parity and risk among siblings
Epidemiological
Sleeping position, bed environment and bed sharing
Prone sleep position has been shown to greatly increase the risk of SIDS, especially in infants who sleep in a soft bed and/or share a bed with the parents.
Pre-natal care
Overheating
Altitude
Greater altitude has been linked to increased rates of SIDS
Race and Ethnicity
American Indian and non-Hispanic black infants have been shown to have an increased risk to die from SIDS

*Topics that were not explained in detail have controversial data and as such no clear link has yet been established between these factors and the occurrence of SIDS

PATHOPHISIOLOGY

TRIPLE RISK HYPOTHESIS

SIDS has always been considered to have a multifactorial pathway. In 1994, the triple risk hypothesis was postulated, which proposes that SIDS results from three overlapping factors: a vulnerable infant, a critical developmental period in homoeostatic control and an exogenous stressor (Figure 2). Since then, this has been the most widely accepted model. Based on it, SIDS only occurs when a vulnerable infant is exposed to an exogenous stressor and lacks the proper defense mechanism to deal with it. Therefore, all factors must be present for a death to occur [15].

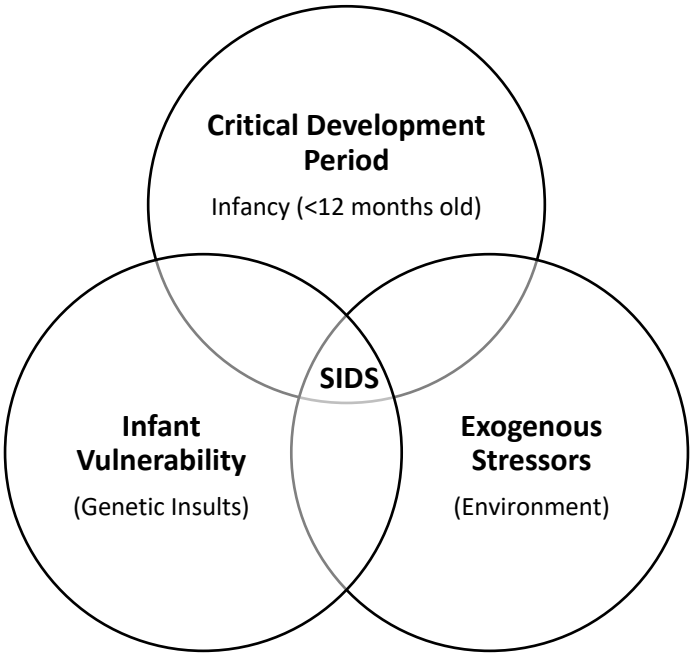

Figure 2 – The triple-risk hypothesis for SIDS. (adapted and taken from [16])

In 1970, the first report of karyotype abnormalities in 10 infants was published, suggesting that SIDS might have a genetic background [17]. Since then, variants in genes associated with regulation of the central nervous system, immune system function and inherited cardiac conditions have been proposed as the underlying condition for an infant's vulnerability to SIDS [18].

DEFECTIVE NEURONAL DEVELOPMENT AND RECEPTOR DEFICIENCY

Studies have shown that infants who died from SIDS displayed delayed development of the brain stem and a significant lower degree of myelination in certain regions of the brain. Further studies from these brain stems have shown abnormalities in muscarinic, kainite and lysergic acid receptors, particularly in the nuclei that is responsible for the control of cardiorespiratory response to stimuli. Moreover, genetic polymorphisms in the medullary serotonin system (5-HT), which is believed to have a major role in the regulation of the cardiorespiratory system through the autonomic nervous system, have also been identified in SIDS cases [19–22].

IMMUNE SYSTEM DYSFUNCTION AND INFECTION

SIDS can occur any time before 1 year of age. However, it has a peak incidence between 2-4 months old, which corresponds to the time when the passive immunity from the mother decreases, leading to the activation of the infant's immune system. During this time, not only can the infant be briefly vulnerable to lethal infections, but this immune system activation may also generate a confined immune response, specifically to irritating agents of the respiratory tract as well as infectious agents, which has the potential to create bronchospasm, pulmonary edema, and cytokine-mediated outcomes (eg. fever). Moreover, elevated concentrations of IgG, IgM, IgA and IL-6 have also been detected in SIDS cases [3].

The pathogen most associated with SIDS is the respiratory syncytial virus. Therefore, it's not surprising that during winter, especially during viral epidemics in a community, the incidence of SIDS increases [3].

CARDIAC GENETIC SUSCEPTIBILITY

In the last few years, genetic studies have provided clues to the cause of death in some SIDS cases and they altogether suggest that 10-15% up to one third of these might be explained by inherited cardiac diseases not detectable during conventional forensic autopsy investigations (Table 3) [23–25]. The most investigated genes in SIDS correspond to primary electric disorders of the heart (channelopathies) and it has been shown that nearly 1 in every 5 SIDS cases carries a mutation in genes encoding cardiac ion channels, with the vast majority having a malignant phenotype [26]. Although they are less frequent, mutations in genes related to structural abnormalities in the heart (cardiomyopathies) have also been shown to play a role in SIDS, specifically, in those that encode sarcomeric proteins [6].

Table 3 – Genes with mutations associated with SIDS. (taken and adapted from [27])

Disease	Gene	Encoded Protein	Frequency in SIDS (%)
LQTS1	KCNQ1	K_V7.1 potassium channel α-subunit	1,0
LQTS2	KCNH2/HERG	K_V11.1 potassium channel α-subunit	0,5
LQTS3/BrS1	SCN5A	Na_V1.5 sodium channel α-subunit	4,8
LQTS6	KCNE2	MiRP1 potassium channel β-subunit	0,5
LQTS9	CAV3	Caveolin 3	1,5
LQTS10	SCN4B	$Na_V\beta$4 sodium channel β-subunit	0,3
LQTS12	SNTA1	α1-syntrophin	1,0
CPVT1	RYR2	Cardiac ryanodine receptor	1,5
BrS2	GPD1-L	Glycerol-3-phosphate dehydrogenase 1-like sodium channel interacting protein	0,9
BrS7	SCN3B	$Na_V\beta$3 sodium channel β-subunit	0,7
BrS8	KCNJ8	Kir6.1 potassium channel α-subunit	0,7
	GJA1	Cx43 gap junction protein	0,3
HCM	MYBPC3	Cardiac myosin-binding protein C	0,6
HCM	TNNI3	Cardiac troponin I	0,3

INHERITED ARRHYTHMIA SYNDROMES

In the heart, the relationship between sodium, calcium, and potassium ionic currents results in a heartbeat. In order for these ions to cross the myocardial membrane, they need to use specific ion channels. Therefore, mutations in genes that encode these specific channels or proteins associated with these channels may impair ionic conduction, leading to congenital cardiac channelopathies, which may culminate in life-threatening ventricular arrhythmias. These inherited arrhythmia syndromes are an important cause of SCD in the young and, in most cases, the autopsy is typically negative, since the heart is usually structurally normal with no signs of disease macroscopically. Recent genetic studies have identified mutations in genes associated with cardiac channelopathies, permitting diagnosis in the deceased using postmortem genetic testing [5, 28, 29].

The major cardiac channelopathies include long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) [30]. However, this review will only focus on the long-QT syndrome and the Brugada syndrome.

LONG-QT SYNDROME

LQTS comprehends a distinct group of cardiac channelopathies characterized by delayed repolarization of the myocardium and the presence of a prolonged QT interval on a 12-lead surface electrocardiogram (ECG), after secondary causes are excluded, such as QT-prolonging medications and electrolyte or metabolic abnormalities. Since the QT interval varies inversely with cardiac frequency, the measurement of the QT interval is usually corrected for heart rate (QTc) using various formulae (eg, the Bazett formula: $QT/RR^{1/2}$). While in adolescence, the normal QTc range is 370–440 ms (being the same in males and females), in adulthood, the normal upper limit for the QTc is 450 ms in men and 470 ms in women [31]. Table 4 presents the normal, borderline, and prolonged QTc values calculated by the Bazett formula according other authors.

Table 4 – Evaluation of the QT interval. (taken and adapted from [32])

QT interval correction method (formulas)	
Bazett	$QT/RR^{1/2}$
Fridericia	$QT/RR^{1/3}$
Framingham	QT + 0.154 (1000 – RR)
Hodges	QT + 105 (1/RR – 1)

Normal, borderline, and prolonged QTc values calculated by the Bazett formula			
	Normal	Borderline	Prolonged
1-15 years-old	< 440 ms	440 – 460 ms	> 460 ms
Adult (male)	< 430 ms	430 – 450 ms	> 450 ms
Adult (female)	< 450 ms	450 – 470 ms	> 470 ms

The European Society of Cardiology (ESC) guidelines of 2015 suggested the criteria of a QTc ≥ 480 ms in an asymptomatic patient or a QTc ≥ 460 ms in the presence of unexplained syncope to be used as the diagnostic basis of LQTS [1]. However, some individuals with LQTS may not manifest QTc prolongation on the ECG. Since these patients are at risk of a polymorphic ventricular tachycardia called Torsade de Pointes, which can induce episodes of syncope and culminate in SCD, complete evaluation based on personal history, family history, and various electrocardiographic studies are warranted in order to properly establish this diagnosis [4].

Congenital LQTS is a genetically heterogeneous disorder usually inherited in an autosomal dominant mode that can be responsible for approximately 3,000–4,000 SCDs in childhood in the US, with an estimated prevalence of 1:2,500 persons [31]. At present, 17 genetic variants have been associated with different types of LQTS (Table 5). However, 3 main genotypes account for over 90% of genetically confirmed LQTS cases: LQTS1 (comprises for approximately 55% of the cases), LQTS2 (responsible for nearly 30% of the cases) and LQTS3 (which constitute around 5-10% of the cases). The additional minor LQTS genes cover less than 5% of LQTS cases [33].

Table 5 – Congenital LQTS subtypes. (taken and adapted from [34, 35])

Name	Gene	Protein	Current	Effect on Function	Frequency
Autosomal dominant inheritance (Romano-Ward)					
LQTS1	KCNQ1	$K_V7.1$	I_{Ks}	(-)	40-55%
LQTS2	KCNH2	$K_V11.1$	I_{Kr}	(-)	30-45%
LQTS3	SCN5A	$Na_V1.5$	I_{Na}	(+)	5-10%
LQTS4	ANKB	Anquirin-B	↓ coordination of the exchanger NCX, ATPase Na^+/K^+	(-)	Rare
LQTS5	KCNE1	MinK	I_{Ks}	(-)	Rare
LQTS6	KCNE2	MiRP1	I_{Kr}	(-)	Rare
LQTS7	KCNJ2	Kir2.1	I_{Kl}	(-)	Rare
LQTS8	CACNA1C	$Ca_V1.2\alpha1$	I_{CaL}	(+)	Rare
LQTS9	CAV3	Caveolin-3	I_{Na}	(+)	Rare
LQTS10	SCN4B	$Na_V\beta4$	I_{Na}	(+)	Very Rare
LQTS11	AKAP9	Yotiao	I_{Ks}	(-)	Very Rare
LQTS12	SNTA1	Syntrophine-α1	I_{Na}	(+)	Very Rare
LQTS13	KCNJ5	Kir3.4	$I_{K\text{-}Ach}$	(-)	Very Rare
LQTS14	CALM1	Calmodulin 1	Signaling dysfunction Ca^{2+}	?	Rare
LQTS15	CALM2	Calmodulin 2	Signaling dysfunction Ca^{2+}	?	Rare
Autosomal recessive inheritance (Jervell and Lange-Nielsen)					
JLN1	KCNQ1	$K_V7.1$	I_{Ks}	(-)	Rare
JLN2	KCNE1*	MinK	I_{Ks}	(-)	Rare

*: mutations in the KCNE1 gene can cause either the Roman-Ward syndrome (autosomal dominant; LQT5) or, if in homozygosity or composite heterozygosity, Jervell and Lange-Nielsen Syndrome (autosomal recessive); I_{Ks}: delayed rectifier component of the K^+ I_{Ks} current ("delayed rectifier"); I_{Kr}: fast component of late rectification (internal rectification - K^+ channels are open when a potential is negative and closed when potential is less negative or positive) of I_{Kr} (delayed rectifier) current; I_{Na}: Na^+ current dependent on voltage; I_{Kl}: K^+ input current, rectifier; I_{CaL}: currents through voltage-dependent L-type calcium channels; $I_{K\text{-}Ach}$: K^+ current regulated by acetylcholine receptors; (-): loss-of-function; (+): gain-of-function

LQTS1 is caused by a loss-of-function mutation in KCNQ1-encoded $K_V7.1$ channel subunit of the voltage-gated potassium channel that mediates the slow component of the delayed rectifier potassium current (I_{Ks}). These patients have a T-wave with a wide base in the ECG and typically have syncope or SCD during physical exercise. LQTS2 is related to a loss-of-function mutation in KCNH2-encoded $K_V11.1$ channel subunit that disturbs the rapidly activating component of the delayed rectifying potassium current (I_{Kr}). Patients tend to have T-waves with diminished amplitude on the ECG and characteristically have syncope or SCD with unexpected auditory stimuli or strong emotions. Finally, LQTS3 has been linked to a gain-of-function mutation in SCN5A-encoded $Na_V1.5$ that affects the sodium influx current (I_{Na}) responsible for the depolarization of the myocardium as well as the spreading of the electrical signal through the cardiac musculature. Due to delayed opening of the sodium channel, LQTS3 patients have late-peaked T-waves and long, flat ST segments on the ECG, as well as a tendency towards bradycardia and a higher incidence of SCD during sleep (Figure 3) [33].

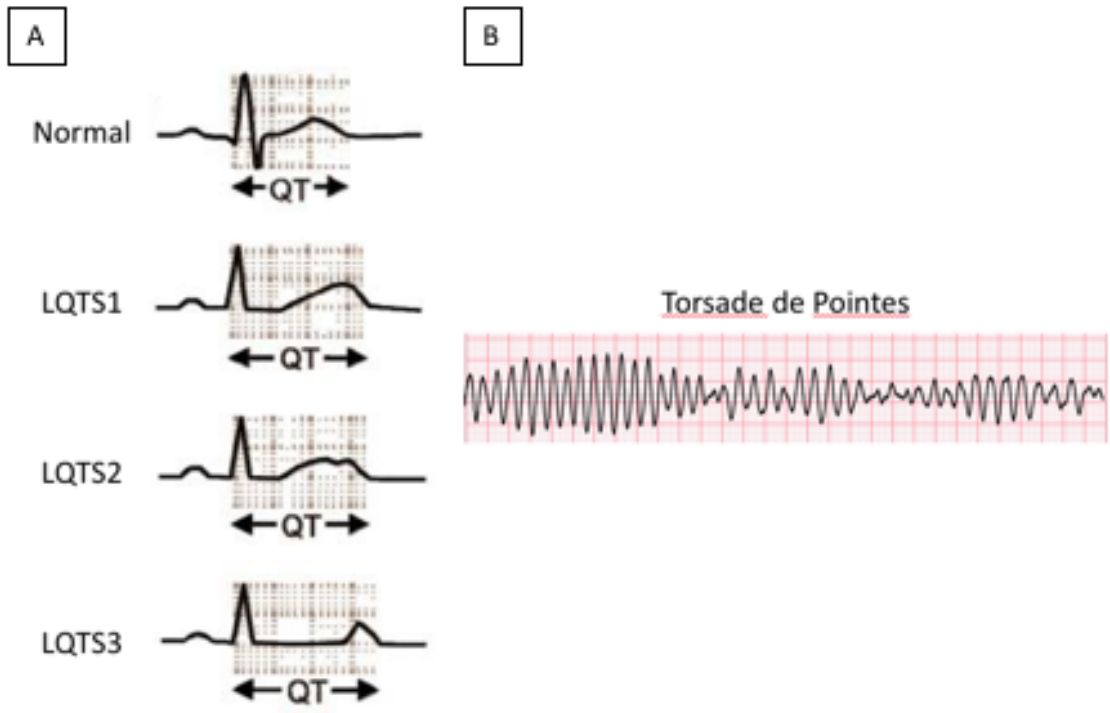

Figure 3 – (A) Most frequent LQTS ECG patterns (QT intervals and morphology); (B) ECG pattern of Torsade de Pointes. (taken and adapted from [34])

The association between ventricular tachyarrhythmia in infants and channelopathies has been studied for a very long time. In 1998 a study was published where the authors analyzed the ECGs of nearly 35,000 newborns and found that babies with prolonged QTc had a higher prevalence of SIDS. Further statistics have shown that this prolonged QTc interval was observed in 30-35% infants who died from SIDS during the 1st week of life. Since then, several studies have been performed in order to establish a connection between genetic mutations associated with LQTS and SIDS (Table 6) [3, 36–49].

One longitudinal study has shown that the QTc interval increases during the 2nd month of life, particularly in male infants with an odds ratio of 47:1, returning to basal levels found at birth by the 6th month. Therefore, in order to detect LQTS that might lead to SIDS, an ECG can be performed during the 2nd or 3rd week of life, since the risk of SIDS and of deceitful long QT intervals (false positives) is enormously reduced. Even though 20-25% of the families meeting clinical diagnostic criteria for LQTS do not have demonstrable pathogenic variants in one of the above-mentioned genes, genetic studies are still warranted since the underlying genetic basis heavily influences the response to the standard LQTS pharmacotherapy, the β-blockers. These agents are extremely protective in LQTS1 patients, moderately protective in LQTS2, and offer no protective benefit in patients with LQTS3. The mechanism responsible for this benefit is considered to be a decline in sympathetic tone that prevents prolongation of the QT interval. Another efficient anti-adrenergic therapy is left cardiac sympathetic denervation. This therapy is particularly beneficial in patients where β-blockers are contraindicated or when symptoms have presented even with suitable β-blocker therapy. This procedure has also been used in infants who have exceptionally prolonged QT intervals and are at extreme risk of SCD [3, 4, 31, 50].

Table 6 – Long QT syndrome as a causative factor of SIDS and implicated mutations (taken and adapted from [36])

Study/year	Study type	Total number of cases	Number of SIDS cases with causative mutation	Genes
Wang et al./2014 [37]	Case-control	141	19 (13,4%)	SCN5A KCNQ1 KCNH2 KCNE2
Glengarry et al./2014 [38]	Case-control	102	4 (3,9%)	SCN5A KCNH2 KCNQ1
Horigome et al./2010 [39]	Case-control	58	12 near SIDS (20,6%)	SCN5A KCNH2 KCNQ1
Millat et al./2009 [40]	Case-control	32	5 (15,6%)	SCN5A KCNH2 KCNQ1 KCNE1
Otagiri et al./2008 [41]	Case-control	42	4 (9,5%)	SCN5A KCNH2 KCNQ1
Arnestad et al./2007 [42]	Case-control	201	19 (9,4%)	SCN5A KCNH2 KCNQ1 KCNE2 CAV3
Kato et al./2014 [43]	Case-control	7	4	SCN5A KCNH2
Tan et al./2010 [44]	Case-control	292	1 (0,3%)	SCN4B
Cheng et al./2009 [45]	Case-control	292	3 (1%)	SNTA1
Cronk et al./2007 [46]	Case-control	134	3 (2,2%)	CAV3
Plant et al./2006 [47]	Case-control	133	7 (5,2%)	SCN5A
Lupoglazoff et al./2004 [48]	Case-control	23	3 (13%)	KCNH2
Ackerman et al./2001 [49]	Case-control	93	2 (2,1%)	SCN5A

In conclusion, QTc interval prolongation may be an arrhythmogenic substrate that leads to lethal ventricular arrhythmias, particularly Torsade de Pointes. However, the presence of a trigger is usually required, specifically one that increases cardiac sympathetic stimulation, such as unexpected noise, sleep apnea or exposure to cold. This may be explained by variations in the development of the cardiac sympathetic innervation, which usually only finishes by the 6^{th} month of life. In some cases, there may be a differential development of the right and left sympathetic nerves, which leads to a transitory neural unevenness, leaving the infants susceptible to sudden death when there is an abrupt increase in the sympathetic activity. Still, more studies are warranted in order to determine if the screening for increased QTc interval in the prevention of SIDS will be the best strategy [3].

BRUGADA SYNDROME

In the Brugada syndrome (BrS) patients usually present characteristic resting ECG abnormalities, namely ST-segment elevation in the three right precordial leads V1-V3 (unrelated to ischemia, electrolyte abnormalities or structural heart disease), and often, but not always, an apparent right bundle branch block. This ECG pattern used to be classified into three different types. However, in 2012, a consensus report reviewed the ECG classification of BrS and nowadays it is classified only into two different types (Figure 4) [31, 51].

The Brugada pattern (BrP) type 1, also termed “coved”, shows ST-segment elevation ≥ 2 mm followed by an upward convexity and sudden descent to an inverted T wave, while the type 2, also termed “saddleback”, has a reduced degree of ST-segment elevation and settles into an upright or biphasic T wave [51].

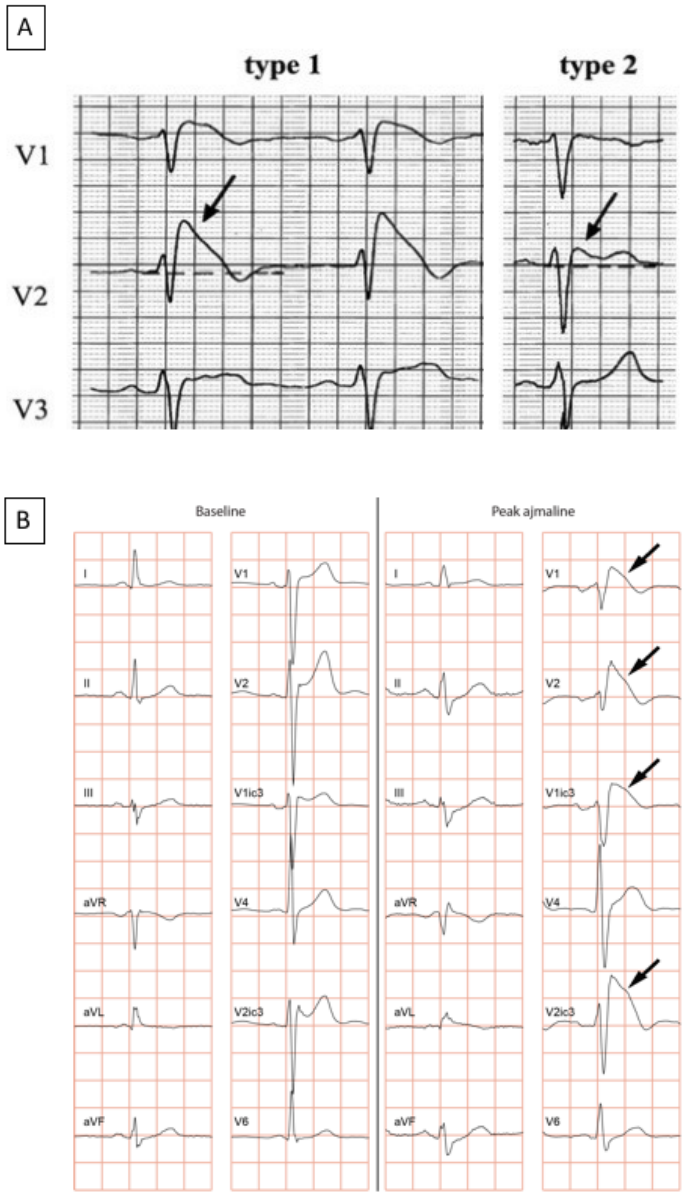

Figure 4 – Electrocardiographic Brugada patterns: spontaneous (A) and after challenge test with ajmaline (B). (taken and adapted from [52, 53])

The ESC guidelines of 2015 suggested the criteria of a ST-segment elevation with type 1 morphology ≥ 2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers as the diagnostic basis of BrS. However, the signature findings of BrS on the ECG can be transient, and subtle changes on the ECG similar to those of BrS can be found in patients without BrS. As such, BrS should be suspected in patients with a type 1 ECG pattern in more than one right precordial lead (V1-V3) if there is documented ventricular fibrillation (VF), polymorphic ventricular tachycardia and family history of sudden cardiac death. Since BrS patients are characterized by an increased risk of syncope, ventricular arrhythmias and SCD it is essential to establish the correct diagnosis [1, 54].

BrS is a cardiac genetic disorder usually transmitted in an autosomal dominant mode (Table 7). The penetrance and expressivity of the disorder are highly variable, ranging from absence of symptoms throughout a normal life span to SCD during the first year of life. The prevalence of this syndrome varies with the population studied, but it has been speculated to be as high as 1:2,000. Men are approximately nine times more frequently affected than women [4, 31, 55].

The BrS has been linked to loss-of-function mutations in genes responsible for the sodium channel (SCN5A; about 25% of the cases) and calcium channel (CACNA1C and CACNB2B; around 10% of the cases) (Table 7). These gene mutations lead to a reduction or loss of sodium or calcium current respectively, thereby reducing the action potential duration, which is further shortened by the fleeting outward I_{to} current. This results in marked heterogeneity of action potential durations across the layers of cardiomyocytes and within the ventricular epicardium, which is the electrical substrate that predisposes BrS patients to ventricular tachycardia and/or fibrillation [4, 55].

Table 7 – Genes mutated in Brugada syndrome. (taken and adapted from [56–59])

Phenotype	Gene	Proteins	Effect on Function	Frequency (%)
Sodium channels and associated proteins				
BrS1	SCN5A	$Na_V1.5$	(-)	11-28
BrS18	SCN10A	$Na_V1.8$	(-)	5,0-16,7
BrS5	SCN1B	$Na_V\beta1$	(-)	1,1
BrS17	SCN2B	$Na_V\beta2$	(-)	<1
BrS7	SCN3B	$Na_V\beta3$	(-)	<1
BrS2	GPD1L	dehydrogenase like-1 of glycerol-3-phosphate	(-)	<1
BrS11	RANGRF	*MOG1*	(-)	<1
BrS15	SLMAP	Sarcolemma associated protein	(-)	<1
BrS20	PKP2	Plakophilin-2	I_{Na} deficit	<1
BrS19	HEY2	$Na_V1.5$	(-)	<1
Calcium channels				
BrS3	CACNA1C	α1c subunit of the voltage-dependent L-type calcium channel ($Ca_V1.2$)	(-)	6,6
BrS4	CACNB2B	B2 subunit of the voltage-dependent L-type calcium channel ($Ca_V\beta2$)	(-)	4,8
BrS10	CACNA2D1	Subunit α2/δ1 of the voltage-dependent calcium channel ($Ca_V\alpha2\delta1$)	(-)	1,8
BrS16	TRPM4	*"Transient receptor potential cation channel subfamily M member 4"*	(-)	<1
Potassium channels				
BrS13	KCND3	Potassium channel voltage dependent-subfamily D member 3	(+)	<1
BrS6	KCNE3	Potassium channel voltage dependent-subfamily E member 3	(+)	<1
BrS9	KCNJ8	Potassium channel inward rectifier 8 ATP dependent	(+)	2,0
BrS14	HCN4	*"Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4"*	(+)	<1
BrS12	KCNE5	Voltage-dependent potassium channel subfamily E "*regulatory* β" subunity 5	(+)	<1
BrS8	KCNH2	$K_V11.1$, I_{Kr}	(+)	1-2
BrS1	ABCC9	SUR2A (2A subunit of the sulfonylurea receptor), IK-ATP	(+)	4-5

(-): loss-of-function; (+): gain-of-function

Even though BrS usually presents in adulthood, targeted molecular autopsy has revealed that some mutations associated with BrS might be responsible for the development of SIDS [27]. One study from 2007 analyzed 228 SIDS cases and found three loss-of-function mutations in GPD1-L, that lead to disturbed channel trafficking, weakening the I_{Na} current [60]. Furthermore, a cohort study from 2010 evaluated 292 SIDS cases and were able to identify three rare missense mutations (two in SCN3B and one in SCN4B) that lead to a significant loss-of-function with decreased peak I_{Na} and increased late I_{Na} [44]. Additional case reported also revealed mutations in SCN5A, SCN1B and CACNB2B in SIDS cases [61–64]. Ventricular arrhythmias in BrS typically happen while resting or sleeping in association with elevated vagal tone and fever, especially in children. Although the risk of ventricular arrhythmias is usually low in children, these settings might be especially relevant to SIDS [9, 65]. The results from a population based study, where 30 children (<16 years of age) affected by BrS where analyzed, revealed that fever was the most common triggering factor for arrhythmic cardiac events, including syncope and SCD [66].

Since BrS is transmitted in an autosomal dominant mode, first-degree relatives of patients with this syndrome should always be investigated with an evaluation of personal history and an ECG. Despite our advances in comprehending the genetics of BrS, the known susceptibility genes cannot fully explain the clinically diagnosed cases, since most patients (65-70%) do not have mutations in these genes. Therefore, the role of diagnostic genetic testing is currently relatively limited. Nevertheless, if a BrS mutation is identified, family screening is simplified and an implantable cardioverter defibrillator (ICD) placement is recommended for secondary prevention of SCD [31, 55].

CARDIOMYOPATHIES

Cardiomyopathies are disorders characterized by abnormal function and/or structure of the heart, which may lead to arrhythmias. Even though the origin of cardiomyopathies is thought to be multifactorial, it is believed that these diseases may be triggered by genetic mutations in genes that encode structural proteins, such as, desmosomes, sarcomeres, the cytoskeleton and the nucleus envelope [55].

Together with inherited arrhythmia syndromes, cardiomyopathies may be considered one of the major causes of SCD, since they often converge to heart failure. Even though these disorders are often found during the autopsy of a SIDS case, thereby identifying the cause of death and as such the diagnosis is changed to SUID, some cases with mutations in in structural proteins may have no evidence of structural defects but still possess a hidden arrhythmogenic phase thereby maintaining the original diagnosis of SIDS. This clearly highlights the importance of performing an autopsy with molecular evaluation in these cases [6, 67].

Early clinical investigations have documented hereditary transmission for several cardiomyopathies, which suggests a genetic basis of this disease. This hypothesis has now been widely confirmed by intensive research [55].

These disorders are usually categorized according to the morphological subtype, which include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC) [55]. However, in this review we will only focus on the hypertrophic cardiomyopathy, which has been the most associated cardiomyopathy with SUID and/or SIDS.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is characterized by a thickened, but not dilated, left ventricle in the absence of another cardiac or systemic condition, with myocyte disorder and intramyocardial scar. This definition applies to children and adults and makes no *a priori* assumptions about aetiology or myocardial pathology. The myocytes of both the interventricular septum and the left ventricle free wall exhibit peculiar shapes, although they usually maintain the intercellular connections with adjacent cells. Furthermore, the myofilaments are also usually chaotically organized. Autopsy of individuals with HCM has also demonstrated an increased intramural thickening of coronary arterioles, which leads to deformation and reduction of the lumen. It has been hypothesized that these factors contribute to localized silent myocardial ischemia which, in combination with dysfunction of the autonomic nervous system, leads to the genesis of ventricular tachycardia (VT) which may culminate in ventricular fibrillation (VF) and SCD. This theory has been proven by the demonstration of the presence of fibrosis in cardiac MRI, which is an arrhythmic substrate [68–70].

The diagnosis of HCM is mainly performed by resorting to imaging techniques. The 2014 ESC guidelines suggest different diagnostic criteria of HCM according to patient age. In adults, HCM is diagnosed by a wall thickness ≥ 15 mm in one or more left ventricular myocardial segments, regardless of the imaging technique used (echocardiogram, cardiac magnetic resonance (CMR) or computed tomography (CT)), that cannot be explained exclusively by loading conditions (Figure 5). Some disorders, both genetic and non-genetic, may present with a lesser extent of wall thickening (13-14 mm) and in these cases, the diagnosis demands evaluation of family history, symptoms unrelated to the heart, ECG anomalies, laboratory tests and other imaging techniques. In children, HCM is also diagnosed by wall thickness, when its value is two times greater than the standard deviation of the predicted mean. Besides the typical increase in wall thickness, other morphologic abnormalities may also be found and should be considered, such as, myocardial fibrosis, structural irregularities in the mitral valve and altered coronary microcirculatory function [71].

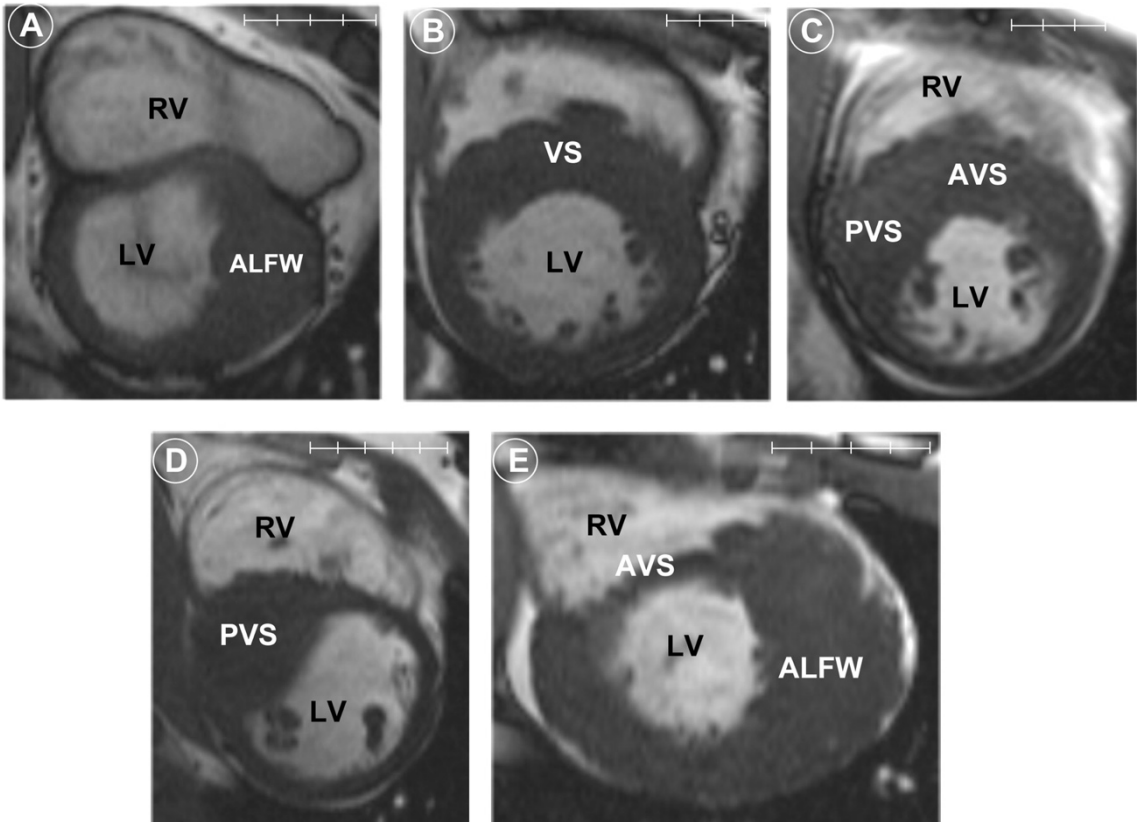

Figure 5 – Diverse patterns of LV hypertrophy encountered in HCM shown in CMR short-axis images at end diastole: (A) anterolateral free wall (ALFW) hypertrophy; (B) moderate hypertrophy involving only anterior and posterior portions of ventricular septum (VS); (C) posterior ventricular septal hypertrophy (PVS) extending into contiguous anterior ventricular septum (AVS); (D) hypertrophy of the posterior portion of ventricular septum (PVS) (E) massive confined to anterolateral free wall (ALFW) but also involving cposterior free wall and anterior ventricular septum (AVS). (taken from [70])

HCM is one of the most common inherited cardiac structural diseases, with an estimated prevalence of 1:500 in the general population. Furthermore, it is also the most common cause of SCD in the young, especially in athletes. HCM is transmitted in an autosomal dominant mode with variable penetrance, and it has been linked to mutations in genes encoding cardiac sarcomeric proteins in 40-60% of the cases while other 5-10% are associated with other genetic disorders, inherited metabolic and neuromuscular diseases and chromosome abnormalities (Figure 6) [71–73].

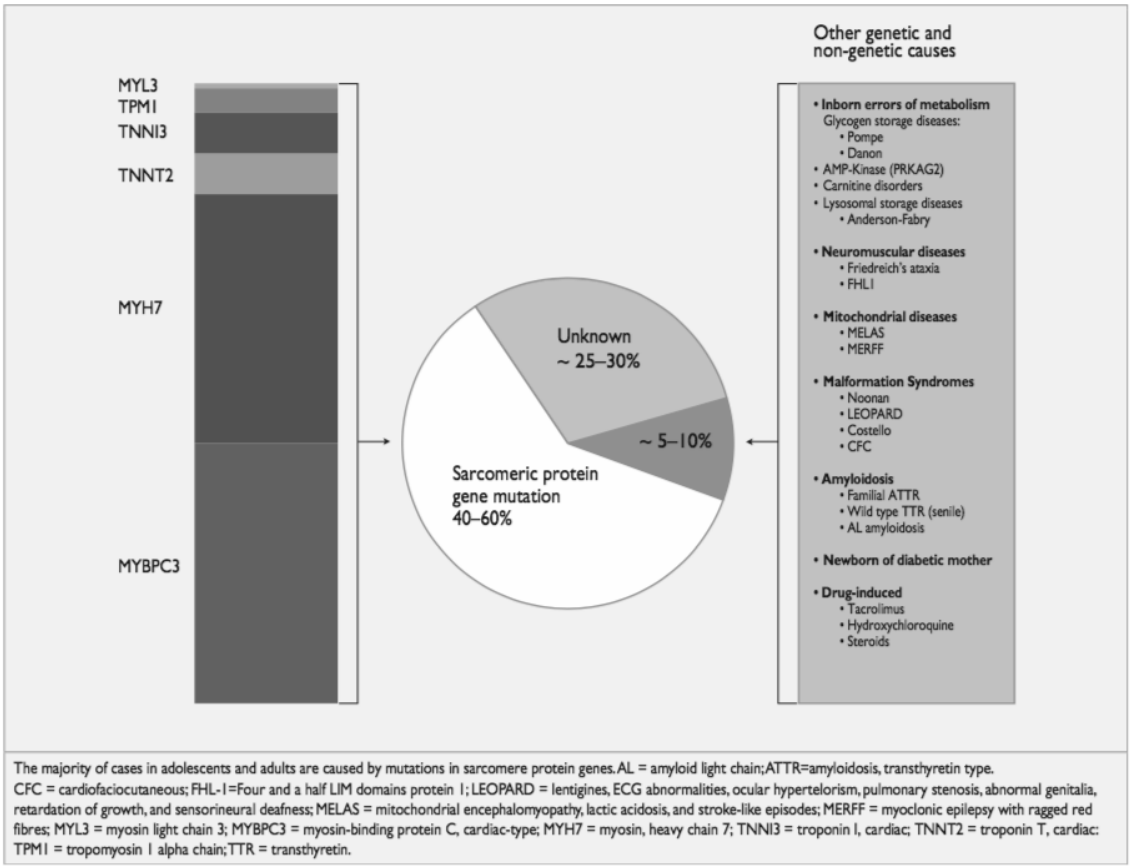

Figure 6 – Diverse aetiology of hypertrophic cardiomyopathy. (taken from [71])

Overall, 1,500 mutations in at least 11 genes have been implicated. However, the majority of the genotype-positive individuals with HCM have mutation in the β-myosin heavy chain (MYH7) or the myosin-binding protein C (MYBPC3) (Figure 5) [72, 73].

The muscle myosin is a hexameric protein, which contains two light chain, two heavy chain and two regulatory light chain subunits. The MYH7 gene encodes the β heavy chain subunit of cardiac myosin. Even though the precise mechanism by which mutations in this gene lead to HCM is still uncertain, most of the MYH7 mutations seem to result in amino acid substitutions in the globular head of myosin, which involves the binding sites of ATP, actin and the regulatory light chains. Therefore, these mutations have been associated with decreased shortening maximum velocity and decreased isometric force generation, which may lead to compensatory hypertrophy. On the other hand, MYBPC3 encodes the cardiac isoform of myosin-binding protein C, which does not contribute directly to force generation, but modulates the contractile performance of

cardiac muscle through interactions with myosin and titin. Most of the mutations in this gene are insertions and deletions, which lead to the generation of a premature termination codon, resulting in proteins that lack the myosin and/or titin binding sites. Studies have shown that cardiac muscle fibers from patients with HCM and positive for MYBPC3 mutations have increased calcium sensitivity which leads to reduced sarcomeric contractility [69, 74, 75].

Cardiomyopathies have also been studied in the setting of SIDS, although they are less frequent than inherited arrhythmia syndromes. Two studies from Brion et al. evaluated mutations in HCM-associated genes than encode sarcomeric proteins in SIDS cases [76, 77]. The most recent one analyzed 286 SIDS cases and found rare genetic mutations in ten cases, three of which were predicted to be functionally significant and with no macroscopic signs of disease, suggesting that these genes could be associated with SIDS. However this study did not have enough linkage data in order to prove causality [77].

Even though genetic mutations have been well established in the pathogenesis of HCM, the diagnostic yield of sarcomere gene testing, which comprises up to nine genes, has been reported to be about 60%. This mainly depends on the selection of patients, since the yield usually decreases to nearly 30% when sporadic cases of HCM are being studied rather than familial cases [78]. Furthermore, it is uncertain whether or not single mutations are enough to cause SIDS. It is more likely that double or compound mutations with macroscopic signs of disease during the autopsy, such as structural abnormalities, are responsible for the early onset of disease, changing the diagnosis from SIDS to SUID [79].

Nevertheless, there is no doubt that cardiomyopathies play a major role in SIDS cases. Either morphologic changes are found during autopsy, thereby including these cases in SUID or, if no histological and/or immunohistochemical alterations are found in the post-mortem analysis, genetic investigations can be important to elucidate whether or not genetic mutations associated with cardiomyopathies could be the potential cause of death [80].

MOLECULAR AUTOPSY

When a parent loses a child to SIDS, there is no doubt that it is a shattering event for not only them, but to the family and the community as well. The most stressful and disturbing characteristic of this experience is the lack of an identifying cause, which could offer these parents some relief. In the last few years, molecular genetic testing (i.e., molecular autopsy) has been one of the major contributors to elucidating the cause of death in these cases, since they have shown that both inherited primary arrhythmias and cardiomyopathies may play a role in these events. Furthermore, molecular autopsy may also reveal the impact on the clinical and genetic assessment of the surviving, and still at risk, family members [81].

Most molecular studies are based on the Heart Rhythm Society/European Heart Rhythm Association (HRS/EHRA) guidelines, which recommend the use of molecular autopsy in SIDS cases if the evidence is leaning towards a clinical diagnosis of LQTS or CPVT, focusing on the 3 major LQTS-associated genes KCNQ1, KCNH2, SCN5A and the CPVT-associated gene RYR2. Furthermore, mutations in the SCN5A gene have also been associated with BrS, which is therefore being tested simultaneously. Even though this panel only focus on channelopathies, authors of independent studies have also suggested the inclusion of cardiomyopathy-associated genes in these analyses [25, 28].

Despite the initial reported detection rates, it has been shown that the diagnostic yield of molecular autopsy can range from 0-35%, being greatly affected by the type of DNA obtained (blood vs paraffin-embedded tissue), the definition of SIDS used, distinctive protocols regarding autopsy procedures and disparity in the interpretation of DNA variants in terms of pathogenicity [81].

Even though the molecular autopsy has been limited to the 4 targeted genes of channelopathies, recent advances in next-generation sequencing (NGS) has expanded the identification of potentially pathogenic mutations using relatively smaller quantities of DNA at a reduced cost. This includes sequencing the protein coding exons of all 22, 000 genes, i.e. whole-exome sequencing (WES), which allows not only genetic testing of all major disease-associated genes, but also less frequently involved or new genes and even discover other genomic regions of significance. Therefore, this technique could help investigating diverse pathogenic mechanisms of the genetically heterogeneous SIDS-associated pathologies, as an unbiased screening test [24, 25, 82].

Despite all the advantages that WES can bring, there are still some challenges inherent to the use of this technique. The most important one may possibly be the determination of which DNA alterations are more likely to be pathogenic and the fact that emerging multigenic models of disease point to the cumulative contribution of several mutation to disease rather than a single one. Therefore, the use of WES in the investigation SIDS needs to be performed with care, thoroughly evaluating the research settings in order to completely understand the association between the genetic variants found and their role in the pathogenesis of SIDS [81].

MANAGEMENT OF THE SURVIVING FAMILY

Family management in the setting of SIDS is complex and should be performed by a multidisciplinary specialized approach. It has been shown that clinical evaluation of the family may help uncover the underlying cause in up to 50% of the families in this setting. Therefore, the clinical assessment of the family is of extreme importance, and should be extended to first-degree relatives, obligate carriers and symptomatic relatives. This assessment comprises two levels of evaluation. Firstly, a complete and comprehensive medical and family history should be performed, including physical examination, resting and exercising ECGs and an echocardiogram. Then, depending on the results founds, a further evaluation could be performed using more advanced imaging techniques, such as CMR, as well as a 24h ECG monitoring and pharmacological challenges, especially in patients where the clinical diagnosis points to BrS [28, 81].

The fact that most of the inherited cardiac genetic disorders (> 95%) are transmitted in an autosomal dominant mode shows that the offspring of parents with these diseases have 50% chance of inheriting the same mutation as the parents. Therefore, when a genetic diagnosis is made in a post mortem SIDS case, genetic testing should also be extended to the parents, in order to understand if this DNA variant is indeed inherited or arose *de novo*. If the mutation was indeed transmitted, then genetic testing should be further extended to asymptomatic, and still at-risk, family members, together with a complete medical history. Using the information provided from all these tests, if a diagnosis is established, the follow-up management is dependent on the disease in question. However, if no diagnosis is made, then the relatives of the SIDS case should be followed-up until age 40, since by this time, most of the genetic heart diseases should have a phenotypic expression. Apart from these procedures, family management should also include an ongoing psychological evaluation in order to care for the wellbeing of the families [81, 83].

CONCLUSION

Numerous studies have shown an association between cardiac genetic mutations that might be associated to SIDS, which has led to an improved understanding of the pathophysiology of this disease. Most of these associations are related to inherited cardiac arrhythmias, as well as structural cardiac abnormalities that might predispose to an arrhythmia, despite the lack of structural changes.

The molecular autopsy can sometimes diagnose disease in SIDS cases. However, the diagnostic yield of the detection of the DNA variants is still low, highlighting the importance of a complex and multifactorial approach to these cases. With the advancement of our technology and the availability of WES, the interpretation of genetic mutations associated with SIDS will require effort and will prove to be a huge challenge.

Currently, simultaneous genetic evaluation of the relatives might reveal the way to interpret the genetic variants discovered and their role for clinical use. Yet, more work is still required to advance our knowledge and help understand the genetic background of vulnerable infants, it order to prevent the disastrous event that is SIDS.

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