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Mini-Symposium: Sudden Infant Death Syndrome

Sudden Unexpected Death in Infancy: Biological Mechanisms

Barbara C. Galland[1,*], Dawn E. Elder[2]

[1] Department of Women's & Children's Health, University of Otago, Dunedin, New Zealand
[2] Department of Paediatrics & Child Health, University of Otago, Wellington, New Zealand

EDUCATIONAL AIMS

- To describe the differences in explained and unexplained SUDI
- To review the mechanisms for explained SUDI and potential biological mechanism for unexplained SUDI (SIDS)
- To describe how research into potential biological mechanisms for SIDS fits within the concept of the triple risk model

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SUMMARY

Sudden unexpected death in infancy (SUDI) covers both explained and unexplained deaths. Unexplained cases or SIDS are likely to have multiple neural mechanisms contributing to the final event. The evidence ranges from subtle physiological signs related to autonomic control, to findings at autopsy of altered neurotransmitter systems, including the serotonergic system, a network that has an extensive homeostatic role in cardio-respiratory and thermoregulatory control. Processes may be altered by the vulnerability of the infant due to age, poor motor ability, or a genetic predisposition. The fatal event may occur in response to an environmental stress. A single final physiological route to death seems unlikely. An understanding of the reasons for explained SUDI also reminds us that a thorough investigation is required after each death occurs.

INTRODUCTION

The epidemiology of sudden infant death syndrome (SIDS) has changed since the safe sleep campaigns with the relative percentages of high risk factors such as the prone sleep position, falling dramatically, while bed sharing has gained more prominence [1,2]. Other changes have included an increase in the proportion of SIDS associated with poverty [2,3], alcohol consumption [4], and pre-term infants [1,2,5]. Factors that have retained prominence include maternal smoking in pregnancy [1] the higher mortality in male infants (60%) [1] and mortality peaks from the 2nd to 4th month of life [6] although there has been shift in the median with more infants dying under the age of 2 months. There has been a decrease in the seasonality of SIDS, historically observed more frequently in the colder months [6,7]. Still of major concern are the racial and ethnic disparities in SIDS rates. African Americans [8], American Indians and Native Alaskans [9] and Aboriginal Australians [10] have rates more than two times higher than their respective national averages, and until recently the rate among Māori in New Zealand was 5 times that of non-Māori [11]. However a recent decline in SIDS and among Māori has been reported [12], although the reasons underlying this remain to be determined.

To gain the full picture of sudden unexpected death in infancy (SUDI) both explained and unexplained (SIDS) cases should be considered as both are possible outcomes when any such death is investigated. In this case, the terminology used is Sudden Unexpected Death in Infancy (SUDI). This review will focus on the potential mechanisms for SIDS deaths, but for completeness, mechanisms of death for explained SUDI will also be briefly discussed.

MECHANISMS OF EXPLAINED DEATH IN SUDI

For 20-30% of infants who appear to have died suddenly and unexpectedly (SUDI), a clear cause of death is found either through the clinical history, death scene examination or post mortem. These cases can then be considered explained SUDI deaths.

* Corresponding author. Department of Women's & Children's Health, University of Otago, PO Box 913 Dunedin, New Zealand. Tel.: +64 3 4740999.
E-mail addresses: barbara.galland@otago.ac.nz (B.C. Galland), dawn.elder@otago.ac.nz (D.E. Elder).

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Infection

Sudden and overwhelming infection is a possible cause of sudden infant death. Pneumococcal or meningococcal septicaemia or meningitis can be of particularly sudden onset, especially in the young infant. The diagnosis should be clear at post mortem. As evidence of minor infection may be found in infants who have a final diagnosis of SIDS, the pathologist must establish that the evidence of infection found is of a degree sufficient to explain the death.

Homicide

This must always be kept in mind, especially where there have been other siblings who have apparently died of SIDS. In general, it is thought that < 5% of SIDS cases may in fact be homicide. As intentional suffocation is virtually impossible to distinguish from SIDS at autopsy this diagnosis may not be confirmed unless there are other significant injuries or a confession [13].

Accidental asphyxia

For some infants it is clear after death scene examination that accidental asphyxia has been the mode of death. Infants have been found dead caught in the bars of their cot or found strangled on a stray piece of cord. It is likely that any infant would die if they got themselves into such a situation. For other infants the scene may have been suspicious for accidental asphyxia, for example if the infant was found lying under a parent, but it cannot be proven that the infant's airway was completely obstructed at the time of death. The question then arises as to whether the particular infant was more vulnerable in a potentially unsafe sleep situation than an otherwise normal infant would be. A recent report highlights a number of infant deaths associated with wearable blankets, saddle wraps and swaddling where cause of death was positional asphyxia, mechanical asphyxia or suffocation [14]. The risk of death increases if the swaddled infant is placed in or rolls into the prone position; thus, infants should always be placed in the supine position when swaddled and swaddling should not be used after rolling attempts by the infant (swaddled or unswaddled) are observed [14].

Cardiac arrhythmias

Genetic cardiac channelopathies such as prolonged QT syndrome are thought to account for up to 5% of SUDI deaths. Genetic cardiac channelopathies fall into the class of genetic polymorphisms within SUDI linked directly to a physiological impairment [15]. A family history of sudden death or deafness should be sought and would suggest that other family members should be screened for these disorders by having an electrocardiogram or 24-hour Holter monitoring. A genetic diagnosis for these disorders can be made after death from stored blood but this is still not a routine procedure [16].

Congenital anomaly

Occasionally an infant will die suddenly and unexpectedly and be found at post mortem to have a significant congenital anomaly that has not been recognised in life. Both cardiac and pulmonary anomalies occasionally present for the first time in this way.

Inborn error of metabolism

A small percentage (<1% in the UK) of babies dying of SIDS probably die as a result of medium-chain acetyl co-enzyme A deficiency (MCAD). MCAD or another metabolic disorder should be suspected if the baby had decreased oral intake before death or if there was any unusual smell about the baby. An experienced pathologist will usually suspect a metabolic cause of death at post mortem and arrange for the appropriate diagnostic tests to be done. These deaths should be occurring less often as the diagnosis for many of these conditions (including MCAD) can be made by use of Tandem Mass Spectrometry on blood collected for screening in the newborn period [17].

Other

Other disease states that have been discovered through post mortem after sudden death include haematological disorders such as leukaemia, gastrointestinal disorders and intracranial haemorrhage.

POSSIBLE MECHANISMS OF DEATH FOR UNEXPLAINED SUDI (SIDS)

Much research has been undertaken in the last few decades to try to find a reason for the death for infants where the clinical history, examination of the scene of death and post mortem has not found a fatal diagnosis. The triple risk model, first described in 1972 by Wedgwood [18] and later revised by Filiano and Kinney in 1994 [19] is a useful hypothetical working model to explain the occurrence of SIDS (Figure 1). The model depicted in a simple Venn diagram with interlocking circles illustrates that an infant can succumb if faced with three concurrent and critical factors; 1) an intrinsic vulnerability 2) a critical developmental period, and 3) an external stressor. Still robust in 2014, this model remains applicable despite changes in epidemiology and advances in technology that have raised the profile of molecular and genetic factors among the potential pathways leading to SIDS. One of the clear messages from the multitude of research studies conducted so far has been that infants who die suddenly and unexpectedly do have some common characteristics.

The vulnerable infant

The infant in this category has an underlying vulnerability/abnormality. They have an intrinsic risk factor associated with that vulnerability that for the most part is not modifiable. The intrinsic risk factors include prematurity, male gender, indigenous ethnicity, poverty, adverse prenatal factors such as maternal smoking or alcohol use during pregnancy, and genetic polymorphisms. Some of these are discussed in more detail below.

Genetic alterations

Genetic causes implicated in unexplained SUDI (SIDS) are classified as genetic alterations with predisposing effects, suggest a predisposition to SIDS vulnerability [15]. This class of genetic factors are predominantly involved in autonomic nervous system or immune system regulation. Several studies have shown specific genetic alterations to be more common in SIDS infants than controls [15].

i) The serotonergic system. A brainstem abnormality of the serotonergic (5-HT) system is implicated as being defective in SIDS. Regarded as one of the most plausible hypotheses in the mechanistic pathways mediating sudden death, abnormalities have been found in genetic mutations, variations in frequencies of serotonin transporter genes, and in serotonin receptor binding. Postmortem tissues from infants that died of SIDS show an increased density of 5-HT neurons in the brainstem, along with decreased expression of 5-HT receptors [20]; these