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The Role of Infection and Inflammation in Sudden Infant death Syndrome

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Abstract

Sudden Infant Death Syndrome (SIDS) is the most common cause of post-neonatal mortality in the developed world. The exact cause of SIDS is likely to be multifactorial involving a critical developmental period, a vulnerable infant, and one or more triggers. Many SIDS infants have a history of viral illness preceding death. Prone sleep position, one of the leading risk factors, can increase airway temperature, as well as stimulate bacterial colonization and bacterial toxin production. Markers of infection and inflammation are often found on autopsy along with microbial isolates. Although the causal link between infection and SIDS is not conclusive, there is evidence that an infectious insult could be a likely trigger of SIDS in some infants.

Introduction

The most common cause of post-neonatal infant mortality in the developed world is Sudden Infant Death Syndrome (SIDS) (1). It occurs in infants from 1 to 12 months of age, with peak incidence between 2 and 4 months. The diagnosis of SIDS is one of exclusion that involves a thorough death-scene investigation, review of the clinical history, and complete autopsy (2,3). Postmortem investigations have become increasingly sophisticated and currently use many advanced biomedical techniques to examine markers of inflammation, virology, bacteriology, toxicology, and metabolic status (4,5).

Most of what is currently known about SIDS causality comes from the identified risk factors found through epidemiologic study. However, while individual risk factors may be linked to SIDS, they are not deemed to cause sudden death; they only increase susceptibility. The exact cause of SIDS is still hypothetical and because of its complexity is considered to be multifactorial. Current paradigms of causality consistently involve three overlapping elements: a critical developmental period, a vulnerable infant, and one or more exogenous stressors or triggers (6-10). All three of these factors need to be in place before an infant dies.

Several important risk associations have been linked to infection and inflammation and are likely to be triggers of SIDS (Table 1). Many SIDS infants have a history of a mild viral illness that precedes death but is not thought to be its cause (2,11,12). Increased incidence of SIDS in winter months parallels closely a susceptibility to infections, particularly those of the respiratory tract. Ethnic groups at increased risk of SIDS also exhibit higher incidences of respiratory diseases than lower-risk populations (13). It has been suggested that common bacterial toxins found in the respiratory tract, in association with a viral infection, can cause SIDS in an infant during a developmentally vulnerable period (8,14).

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Prone sleeping has long been associated with increased SIDS risk (1).. Several explanations of causality include impairment of gas exchange leading to hypoxia and hypercarbia; however, there are also data to suggest that a prone position might alter an infant's response to infection. Prone position can increase airway temperature, as well as stimulate bacterial colonization and bacterial toxin production (8,14). Measures of nasal septal temperatures are significantly elevated in the prone compared to the supine sleep position (15). Infants with an upper respiratory infection placed in the prone position for sleeping have been shown to have increased bacterial colonization with Gram-negative bacilli, *Haemophilus influenza* and *Neisseria* species on early morning swabs. The highest bacterial counts were measured in prone sleepers with a concurrent upper respiratory infection (16).

More importantly, the majority of infants dying of non-bacterial causes in the first year of life do not show signs of bacterial colonization, with the exception of SIDS infants. The odds for finding coliforms in the respiratory tract of a SIDS infant are 29 times greater than for a healthy live infant (17). Many SIDS infants have signs of increased bacterial toxin production including pyrogenic staphylococcal toxins, along with signs of increased inflammation and organ shock not seen in infants dying from non-infectious causes (18,19). Interestingly, as more infants sleep in a supine position the association between infection and SIDS has decreased slightly (20).

Markers of infection and inflammation are often found on autopsy in SIDS infants along with isolates of bacteria and a few viruses (20-22). Many of these organisms are capable of increasing inflammation either as superantigens or through endotoxin in their cell wall. In addition, SIDS infants showing histologic signs of shock on postmortem examination were more likely to have cultures positive for *E. coli* than those dying from non-infectious causes (19,23). Although the causal link between infection and SIDS is not conclusive, there are data to show a close association. An aberrant response to an infectious insult is quite likely a trigger of SIDS in some infants.

Autopsy and Infection

In a retrospective analysis of more than 1,500 consecutive postmortem examinations of children between 7 and 365 days of age, 546 presented as sudden unexplained death of infant (22). Of these, the cause of death was further identified in 202 cases, but uncertain in the remaining 344 cases. The component of the postmortem examination that was the most helpful in diagnosis was the histological examination, followed by macroscopic examination, microbiological investigations, and clinical history. Toxicology, radiology and metabolic screening using tandem mass spectrometry were not as helpful. The majority of infection-related diagnoses were identified primarily by histological sampling rather than microbiological analyses, although microbiology aided in a diagnosis for 20% of cases that would have otherwise gone undetected (22).

Postmortem microbiology samples obtained from the blood, cerebral spinal fluid, lung, and spleen were compared in three groups: those with a known bacterial cause of death, those with a non-bacterial cause of death and those still unexplained after thorough investigation. Positive cultures, yielding a single organism (32%) or mixed growth (68%) were found in around 70% of all three groups. Interestingly 19% of the unexplained group grew organisms known to cause septicaemia but these infants did not have an obvious focus of infection which is not uncommon in septic infants under 4 months of age (22).

This finding was significantly different from infants dying from a non-infectious cause who grew more non-pathogenic bacterial cultures (20). Infants known to die from a bacterial illness had the same approximate number of organisms but a much larger percentage of these were considered pathologic. The cultures from infants with an unexplained cause of

death contained *Staphylococcus aureus* (16%) or *Escherichia coli* (6%) more than did those from infants whose deaths were of a non-infective cause. Although many postmortem bacterial cultures in sudden unexplained death of infancy yielded organisms, most of these are unlikely to cause death (20).

These data support the "Common Bacterial Hypothesis" proposed by Morris et al which states that common organisms, bacterial and viral, can cause SIDS (8,14). Viral cultures can be difficult to obtain postmortem (24,25), making it hard to prove a viral association; however, more than half of SIDS infants have been reported to have a recent mild viral illness near the time of death (12,26). More sophisticated techniques of viral identification could prove useful in establishing the connection between viral and bacterial infection.

The idea that the combination of organisms and resulting inflammatory response causes death is not new in the SIDS literature. A mix of two or more bacteria in culture or mixes of bacteria and viruses have been described in SIDS infants (24,26-31). The two most commonly isolated bacteria are *S. aureus* and *E. coli*. Some of the toxigenic bacterial species identified in SIDS have been tested in *in-vitro* models in which additive or synergistic effects have been found among the toxins (32). In an animal model of sudden unexplained death, the combination of influenza and endotoxin was lethal in 12-day old rat pups; neither challenge alone was sufficient to cause much morbidity or mortality (33,34).

Bacterial and viral cultures have not been examined much in postmortem evaluations because of the concern that that the organisms are contaminants and not related to the cause of death. Although this concern may be valid, most of these organisms will no longer continue to grow when a body is stored at 4° C. Furthermore, the production of toxins by these bacteria requires temperatures between 37 and 40° C. Evidence of bacterial toxin release has been found in more than half of the SIDS autopsies described by Blackwell and colleagues (13). These samples were taken from many different countries, and it would be difficult to say that they were contaminants (21). The most likely cause of death in these cases would be the release of inflammatory mediators that contribute to hyperthermia, hypoglycemia, cardiac arrhythmia, and shock (13).

Many SIDS infants have intrathoracic petechiae and liquid blood in the heart (35,36). It has been speculated that these abnormalities may be associated with the infant's efforts to overcome hypoxia and respiratory difficulties, but they could also be due to the problems of coagulation that often accompany infection and inflammation. Several studies have documented mast cell degranulation in SIDS infants. The release of heparin from these granules could explain the presence of liquid blood around the heart and petechiae in the respiratory tract (37,38)

While autopsy findings have varied, signs of inflammation and response to infection have appeared out of proportion to preexisting symptoms (23,39). The increase in inflammatory markers found in SIDS infants indicates that infection and inflammation are a part of the etiology for some SIDS infants, either as a direct cause or the trigger of a lethal event. It might also be indicative of vulnerability in the immune response to an infectious trigger in infants, particularly with those having a certain genetic predisposition (9,40,41). During the age of high risk for SIDS, the immune system, circadian rhythm, and autonomic nervous system control are at a point of change, switching from neonatal characteristics to a more adult form. All three of these systems are involved in the control of infection and the response to changes induced by inflammation. An imbalance in any or all of these systems could predispose to an adverse event.

Genes and Inflammation

Recent studies have focused on genetic factors that are important in homeostasis. These have resulted in candidate genes for SIDS susceptibility in five different areas: 1) genes related to prolonged QT intervals; 2) genes related to serotonin transporter and receptor binding in the brainstem; 3) genes important in the embryology of the autonomic nervous system; 4) genes related to nicotine metabolism; and 5) genes important in control of inflammation (42). This last group of genes includes those regulating inflammation through tumor necrosis factor-alpha (TNF-a), interleukin (IL) -1, IL-6, and IL-10 polymorphisms (13,40,41,43-48).

Obtaining inflammatory cytokine levels on postmortem examination is difficult; however, IL-6 levels in the cerebral spinal fluid are significantly higher in SIDS infants than in those dying from other non-infectious causes (49). If inflammation is an important factor in SIDS risk, then the most likely candidate genes would be those specific polymorphisms responsible for initiating a strong inflammatory response or decreasing the ability to terminate that response.

Inflammatory cytokine genes have been associated with SIDS risk in several ethnic populations. A TNF-α polymorphism that is a variant with high cytokine production was determined in a large Swedish population (46). An IL-1β polymorphism found to have an increased response to toxic shock syndrome toxin was seen more often in the parents of infants who died from SIDS (44). An IL-6 polymorphism, (IL-6 - 174G/C) was associated with SIDS in some populations but not in others (45,47,48). A similar pattern occurred with several IL-10 polymorphisms found in low risk and high risk populations (40,41,43). These data indicate how difficult it is to compare polymorphisms between populations and indicate that genetics is only one aspect of risk.

Blackwell and colleagues compared IL-10 polymorphisms between a high SIDS risk group of Aboriginal Australians and a low-risk Bangladeshi population living in Britain. They found that both groups were genetically similar in regards to IL-10 polymorphisms. The major difference between the two groups was the higher incidence of maternal smoking in the Aboriginal Australians. Smoking exposure significantly reduced the anti-inflammatory effect of IL-10 in leukocytes. There is some speculation to the interpretation of these data; however the most likely cause is a gene-environment interaction with cigarette smoking, a known major risk factor for SIDS (50). Additionally, bacterial and/or viral colonization of infants is often increased with smoking mothers (43,51) All of these factors (infection, heredity, and smoking) contribute to the increased SIDS risk,

Animal studies of Inflammation

The majority of research on the processes involved in inflammation and SIDS has been done in animal models. A good animal model must reflect the lack of symptoms associated with SIDS. Careful consideration must be given to associations between the human condition and the findings in the model. Insults should be plausible and compatible with daily living, and they can not be so severe that they are obviously the cause of the death. Many animals have been used to study sudden unexplained death; however, the majority of research on inflammation, infection and sudden unexplained death has been done in piglet, rabbit, and rat models.

The piglet model has been used to examine respiratory responses to infection and smoking. Pretreatment with nicotine and endotoxin interferes with mechanisms of autoresuscitation and produces prolonged apnea in experimental piglets exposed to subglottic acidified saline solution (52). Nicotine and IL-1β had a similar synergistic effect when the animal was

exposed to intermittent hypoxia (52). Nicotine and inflammatory mediators appear to act as cofactors in hypoxic-ischemic injury (53). Froen and colleagues did not examine the synergy between endotoxin and nicotine; however, their work suggests a relationship between either nicotine or an inflammatory response to infection and lethal apnea (52,53) .

Gastrointestinal pathogens are known to be a leading cause of morbidity and mortality in children under the age of 5 years (54). Siarakas and colleagues examined the effects of intravenous administration of six common bacterial toxins on the cardiorespiratory system in 1-3 kg rabbits (55). They observed bradycardia, hypotension, and apnea with sudden death and concluded that under the right conditions, intestinal bacteria could produce toxins that cause inflammatory responses similar to those associated with endotoxin-induced shock (55).

Rat models have been developed to examine both infectious and respiratory insults, and the effects of prenatal nicotine exposure. Lee and colleagues showed that subcutaneous injection of nasopharyngeal bacterial isolates cultured from human SIDS infants were lethal in 21-day old weanling rats. The animals died rapidly without signs of illness (56). When *E. coli* and *S. aureus* were given together mortality occurred much more abruptly, demonstrating a synergy between pathogens.

Several researchers have reported that viral infections can predispose to sudden unexplained death in animal models (57,58). A developmental model of sudden unexplained death in neonatal rats has been used to examine the combination of viral and bacterial insults to produce sudden unexplained death in 12-day-old rat pups. A single insult was not sufficient to cause death; however, when the viral challenge was given two days prior to the bacterial endotoxin injection, it caused 70-80% mortality. There must be a combination of events, one viral and one bacterial, as in the “Common Bacterial Hypothesis” of SIDS, to cause death (33,34).

In this neonatal rat model there was an increase in inflammatory markers and release of reactive oxygen species, causing a drop in blood pressure and a rapid septic shock-like episode inducing death (33,34). Tail cardiovascular measurements confirmed a decrease in blood pressure without a compensatory cardiac response. Histologic examination of tissues confirmed signs of shock which have also been reported on postmortem examination in SIDS infants (19,23,33,34).

This model represents another important component of many theories of SIDS, which is a developmental time of increased susceptibility. Ten- to 12-day-old rat pups were most susceptible to these particular insults while younger and older animals did not die (33,34). This age-related vulnerability occurs during a time of developmental changes in autonomic control in rats and a normal decrease in cortisol response to stressors. When these animals were additionally exposed to nicotine during gestation this susceptibility was accentuated (unpublished data). Both infection and nicotine can change how the body responds to infection and inflammation. Prenatal nicotine exposure has the added effect of dampening the autonomic response to hypotension and cardiovascular stress, and thereby increases mortality (59). The mechanisms associated with nicotine and endotoxin mortality are currently being examined in our laboratory.

Understanding the question of age risk is difficult. SIDS occurs between 1 month and 1 year, with peak incidence between 3 and 4 months of age (60). There are numerous developmental times of potential susceptibility as an infant matures. If the infant is challenged during a period when he or she cannot mount a protective response, a lethal event could transpire in response to a common insult. Developmental vulnerability is an important theme in most theories of SIDS.

Maternal Smoking

Maternal smoking is a risk factor for many poor neonatal outcomes. Although passive exposure to environmental tobacco smoke is considered detrimental (61,62), the risk of SIDS doubles with maternal smoking and is 3 to 4 times higher if the mother smokes more than 10 cigarettes per day (63). Maternal smoking during pregnancy is now considered the number one risk factor for SIDS (50,61,64-67).

Prenatal exposure to nicotine affects the development of autonomic responsiveness and alters its maturation (68). It also has an effect on neurotransmitter function and developmental changes in catecholamine production (69). Prenatal nicotine has been shown to impair respiratory function (70,71), and diminishes protective responsiveness to hypoxia in neonatal rats during the first week of life (68,72,73). Animal models also indicate that prenatal nicotine exposure changes the development of sympathetic receptors the heart (74).

Exposure to cigarette smoke could change the response to infectious insults in two important ways. Nicotine exposure increases the inflammatory response to an infectious challenge (75,76), and it alters the development of a protective sympathetic response to a cardiorespiratory event induced by inflammatory mediators (59,77). In order to study some of these features, we are currently examining the relationship between perinatal nicotine exposure, autonomic nervous system development, and endotoxin-induced shock in suckling rats.

Conclusion

It is highly likely that infection and inflammation have a role in SIDS deaths. It would be ideal if we could find a single organism or combination of organisms to blame; however, if it were that simple, the etiology of SIDS would already be known. SIDS is multifactorial, and the death of an infant probably involves a series of conditions. Infants between 2 and 6 months of age appear to have a vulnerable time point when they may not be able to respond effectively to cardiac and respiratory challenge. This might result from damage to the autonomic nervous system or brainstem from nicotine exposure during gestation, or from a specific genetic polymorphism, or from gene-environment interactions. Alternatively, this vulnerability might just be a normal developmental stage during the maturation of the immune and/or neurologic systems.

When vulnerable infants are challenged by infectious toxins, pyrogens, heat stress, hypoxia, or hypercarbia, they are unable to mount a protective response. Many infectious toxins induce hypotension and challenge the cardiovascular system. In animal models, rat pups appear to be dying from uncompensated shock. This is also a distinct possibility in human infants dying of SIDS.

The concept that shock constitutes a factor in SIDS pathology is not new (78-80). Parents have often described their infants as “listless” or “droopy” with increased sweating at the time of death (81,82). During infancy, increased sweating is unusual, and indicates a response to an abnormal event such as heat stress, infection, vasomotor instability, or cardiovascular shock. These symptoms suggest that SIDS infants are not normal prior to death, and that shock might be involved in the events leading to death (83-85).

SIDS continues to be a baffling condition. Infection and inflammation are very likely to have a role in its etiology. Treatments such as supine sleep position could be helpful because they decrease the infant’s exposure to bacterial toxins. Pacifier use and fans blowing in the room have recently been reported to decrease the incidence of SIDS (86-88). Pacifier use could change autonomic responses, and a fan in the room may help maintain a reasonable

room temperature (87,89). Fan use has been found most beneficial with infants in the prone position even though the prone position is not recommended for sleep (87). At the moment the effect of these therapies on SIDS incidence remains unknown. It is, however, likely that some SIDS is caused by interactions between infection by common microbes and normal developmental changes, exacerbated by common insults such as perinatal nicotine exposure.

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Table 1

Summary of research findings associated with infection and inflammation in SIDS

	Relationship to Inflammation and Infection	Citation
EPIDEMIOLOGY		
Prone sleep	Increases naso-pharyngeal temperature, bacterial colonization, and toxin production	(8,14-16)
Maternal smoking	Prenatal smoke exposure changes how an infant responds to inflammation. Second hand smoke increases the inflammatory responses.	(50,61,64-67)
Concurrent illness	A mild viral illness is often described prior to death.	(2,11,12,26)
High Risk Groups	Certain high risk ethnic groups have higher respiratory illness rates.	(13)
POSTMORTEM		
Microbes	Increased coliform species isolated	(17-20,22)
	Viruses isolated	(23,24)
	Combinations of microbes isolated in the same infant (bacterial and viral).	(24,26-31)
Inflammation	Gross pathology and histology indicative of inflammation and shock in SIDS infants.	(19,21,23,39)
	Significantly elevated IL-6 in CSF of SIDS infants.	(49)
	Activation of the mucosal immune system and HLA-DR in SIDS infants.	(90-92)
GENETICS		
	Differences in pro-inflammatory cytokine polymorphisms (TNF-a, IL-1 and IL-6) are found in specific high risk populations.	(45-48)
	Differences in anti-inflammatory cytokine IL-10 polymorphisms are primarily population specific.	(9,40,41)
MODELS		
	Lethal synergism between bacterial toxins *In vitro*	(32)
	Multiple microbes increase inflammation and death in animal models	(33,34,55-58)
	Nicotine increases inflammation and death in animal models	(53,93,94)