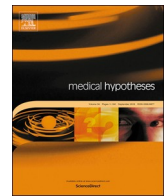




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SIDS, prone sleep position and infection: An overlooked epidemiological link in current SIDS research? Key evidence for the “Infection Hypothesis”

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ABSTRACT

Mainstream researchers explain the etiology of SIDS with the cardiorespiratory paradigm. This has been the focus of intense study for many decades without providing consistent supporting data to link CNS findings to epidemiological risk factors or to the usual clinicopathological findings. Despite this, and the apparent oversight of the link between prone sleep position and respiratory infection, papers citing CNS, cardiac and sleep arousal findings continue to be published. Discovery of the prone sleep position risk factor provided tangential support for the cardiorespiratory control hypothesis which defines the mainstream approach. Despite many decades of research and huge expenditure, no aetiological answer has been forthcoming. In asking why? This paper exposes some of the shortcomings regarding this apparent oversight by mainstream SIDS researchers and examines the role of respiratory infection and puts the case for the “Infection Hypothesis.” In addition, the paper provides encouragement to neuropathologists to examine the potential link between CNS findings and cardiac function (as opposed to respiratory function) in relation to infection and to examine possible correlates between CNS findings and established risk factors such as recent infection, contaminated sleeping surfaces, maternal/obstetric/higher birth, ethnicity, non-breast-feeding, male gender, etc. or with the usual gross pathological findings of SIDS (intrathoracic petechial hemorrhages, liquid blood, congested lungs). The shortcomings exposed through this review invite questions over current research directions and hopefully encourage research into other more plausible hypotheses, such as the infection paradigm.

- Mainstream SIDS researchers appear to have overlooked the key relationship between prone sleep position and infection.
- This omission has major implications for current and future SIDS research.

Background

Mainstream SIDS research has proposed several hypothetical mechanisms underlying these tragic deaths. Because the diagnosis of SIDS is one of exclusion [1], it is unhelpful in unravelling its causation. The list of potential causal mechanisms is long, but the most commonly held hypothesis focuses on homeostatic control of cardiorespiratory function and focuses on sites in the central nervous system which contain the nuclei active in the process of homeostasis. This, in essence, defines the mainstream approach. The hypothesis often invokes a failure of arousal by the infant who is sleeping under conditions of chronic anoxia. The triple risk hypothesis (general vulnerability, age-specific risks and precipitating factors) [2] sustains validity for mainstream researchers given that its elements are broadly applicable and are supported by epidemiological data. However, the data obtained

from studies of the central nervous system and physiology remain insufficient to establish validity [3]. This article re-examines the fundamentals in this regard. Google Scholar and PubMed were used to source key papers. The article dissects and exposes weaknesses in mainstream thought, and proposes an alternative hypothesis. The central argument features the relationship of SIDS to infection. The points raised could lead mainstream researchers to reconsider the directions they have taken.

The hypothesis

This paper sets out a rational hypothesis that SIDS has an inherent and fundamental association with infection and that infection forms the basis for the syndrome's causation. Mainstream research has largely ignored (or is unaware of) the epidemiology that places infection as key

Abbreviations: SIDS, sudden infant death syndrome; SUDI, sudden unexplained death in infancy; CNS, central nervous system; CESDI, Confidential Enquiry into Stillbirths and Deaths in Infancy; FDPs, fibrin degradation products; DIC, disseminated intravascular coagulation

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to answering the SIDS question. Current researchers and paediatric pathologists often refer to Sudden Unexpected Death in Infancy (SUDI) rather than SIDS. When infection is identified in a SUDI case the diagnosis could become Explained SUDI or the diagnosis shifts to “a specified infection in an infant.” If infection causes Unexplained SUDI then pathologists will need some way to diagnose the condition. This is really the main challenge for those who advocate the infection hypothesis. In this regard, sepsis in infancy remains a difficult diagnosis to make in both living infants and those who have died suddenly and unexpectedly. [4] Bacterial toxins have been found in approximately half SIDS/SUDI cases [5–8] and this finding and cytokine profiles together with the strong epidemiological evidence form the basis of the infection hypothesis.

Evaluation of the hypothesis

A heterogeneous pathogenesis?

Mainstream research hangs by this statement: “SIDS has a complex and heterogeneous pathogenesis with multiple abnormalities in a number of physiological functions that may involve neurological, cardiovascular, respiratory, gastrointestinal, nutritional, endocrine, metabolic and immunological systems, with infectious, environmental and genetic components” [9]. While this, as a generality, is true, it begs the question of why do over 90 percent of SIDS cases have very similar pathological findings (intrathoracic petechiae, liquid (unclotted) heart chamber blood, congested lungs and characteristic organ weight findings (large brain and thymus)? [10] Heterogeneous pathogenesis would, on balance of probability, provide a range of pathological findings. Occam’s razor would suggest otherwise and logically impose a single mortal process because of the similarity of gross pathological findings in SIDS cases.

In this regard it behoves mainstream research to reconsider the heterogeneous pathogenesis approach and seriously examine the effect of sepsis/toxaemia and/or an inflammatory state on the brainstem and other brain sites and to examine the existence (or otherwise) of supportive risk factor data which most published CNS studies tend to overlook or have provided little, if any, evidence of correlation [3]. The lack of research into the possibility of underlying sepsis/toxaemia in SIDS is concerning given that sepsis/toxaemia induces apoptosis [11], a common finding in the brainstems of SIDS cases [12]. It would be appropriate, therefore, to examine the CNS of babies dying of sepsis (many of whom are culture-negative) using the same methodologies. Examination of the pathological findings in neonatal sepsis could also be helpful: there remains a serious lack of published information regarding the general and specific morbid anatomical findings in proven neonatal sepsis. For instance, do intrathoracic petechiae occur in neonatal sepsis? A personal communication (Prof. Marta Cohen) attests this.

The role of respiratory viruses

The early SIDS literature is replete with papers demonstrating a relationship between SUDI/SIDS and recent symptoms of respiratory viral infection (RTI). In the 1980’s when the incidence of SIDS was high, there was strong evidence that respiratory viral infection was playing a role as a trigger. The winter peak provided supportive evidence. Interaction between viral RTI, prone sleeping and secondary bacterial changes in the nasopharynx offered a simple and convincing explanation of how sepsis could cause death (see below).

The widespread change in sleeping position (from prone to supine) has coincided with a considerable decline in SIDS/SUDI deaths in most developed countries. The associated seasonality has become less obvious. For a new generation of paediatric pathologists and researchers the link to infection has become less compelling. But SIDS in 2020 is the same disease as SIDS in 1960s and 1980s and it is therefore important

to bring this earlier epidemiological evidence to the attention of current SIDS researchers.

Revisiting the early epidemiology of SIDS could be helpful: in this regard, the most insightful paper by O’Reilly and Whilby [13] deserves special consideration in that it notes the importance of acute respiratory illness in the one to two days before death and the frequent finding of infants in the prone position. The paper should be read by all SIDS researchers for its wisdom and compassion.

Much of the evidence on the role of respiratory viruses was well summarised in the paper by Gold et al. [14]. A shift in thinking that asphyxiation/overlying was responsible for SUDI was seen. The idea was replaced by the notion that respiratory infection was somehow involved in the causal pathway. Unfortunately, the numerous studies [15–22] which attempted to prove the link generally failed, with the exception of Bajanowski et al. [23] whose results favoured an hypothesis that respiratory virus infections could act as a trigger in sudden infant death.

The failure to prove an association in most studies was not because the association did not exist but was by the nature of the studies themselves. Indeed, most have shown a link between viruses and SUDI/SIDS either directly or indirectly through seasonality and a pronounced association with epidemic viral disease [16,19,24]. Proof is impossible when using matched controls because these, almost without exception, show similar rates of virus infection; a not surprising situation because contemporaneous controls simply reflect the viral epidemiology of the time. So those studies were pointless if the authors were seeking a significant difference in rates of infection between SUDI and controls. Similarly, comparison of the degree of inflammatory response is bound to fail [24] given we need to take into account probable differences in pathogenesis. By showing SIDS cases have lesions not considered to be lethal suggests there are different immunopathologic processes involved compared to the histopathology of classical “lethal” pneumonia, bronchiolitis, etc.

The technological advances in viral detection extending from culture, immunofluorescence, and ELISA tests to Nucleic acid detection [20,25] has provided better knowledge as to the viruses causing infection in SUDI (and controls). So far, papers have demonstrated a wide variety of viruses isolated from SUDI/SIDS cases (adenoviruses, RSV, parainfluenza, influenza A, rhinovirus, bocavirus, EBV, HHV6, CMV, VZV, Rubella, etc.) [26,27] The hunt for a specific virus candidate has been fruitless. Because of the difficulty in culturing coronaviruses, only a few studies aimed at these viruses have been published [28,29].

It should be obvious that there is a large number of different viruses identified in SIDS cases. Logically, based on the characteristic common clinicopathological picture, the mechanism behind these “virus-associated” sudden infant deaths is likely to be a single one in which the virus infection acts as trigger clearly involving proinflammatory cytokines (see below).

Interest in cytokine responses to viral infection was stimulated by the work of Howatson who examined IFN- α in SIDS [36]. Further studies followed showing proinflammatory cytokines (IL-1, TNF- α , IL-6) were elevated in SIDS tissues [30–35].

A key paper (cited by Raza and Blackwell) [32] that could have advanced SUDI/SIDS research but was seemingly ignored by mainstream SIDS researchers was co-authored by the Nobel Laureate Peter Doherty [36]; The paper showed that mice infected with lymphocytic choriomeningitis virus (LCM) causes expression of a CD4 T cell receptor that acts as a transgene for induction of fatal haematogenous shock after administration of staphylococcal enterotoxin B (SEB). The toxin was tolerated by uninfected controls. The cytokines TNF, IFN- α , and IL-6 appear to be involved in the pathogenetic process as suggested by Lundemose et al 1993 [30].

The involvement of bacterial toxins and cytokine responses has now been well described in studies that support such a toxigenic shock pathogenetic mechanism in SIDS/SUDI [5–8,37]. Highet et al. [38] showed staphylococcal enterotoxins of several groups were highly

likely to have been involved in SIDS pathogenesis.

The existence now of a good animal model provided by Sarawar et al. [30] for the fatal mechanism involving CD4 priming by virus infection to enhance the lethality of staphylococcal enterotoxin should encourage further research to extend this model to other viruses and bacteriological toxins to provide additional support for the hypothesis.

For reasons that cannot be explained, well-funded mainstream research has preferred to focus on homeostatic mechanisms related to arousal, breathing or cardiac function particularly examining brainstem nuclei and neurotransmitters. The research has revealed some changes in neurones and neurotransmitters in a proportion of cases. The researchers have assumed these changes relate to anoxia but have not examined whether or not infection, exposure to toxins, or proinflammatory cytokines have played a role (see below).

There remains a problem in explaining a number of SIDS deaths which have been observed to be rapid and during which an infant appeared well when put to sleep and was found dead within the next hour. Sepsis would, on balance of probability, be less likely in this instance. There could be an explanation that fits the infection hypothesis: all strains of *Staphylococcus aureus* produce alpha-hemolysin which is a perforin. Pyrogenic toxins are not universally produced by *S. aureus* strains and these toxins induce sepsis. Alpha-hemolysin, on the other hand, is lethal through its action on cardiorespiratory function and could account for sudden death. Given that mutations in channelopathy genes are associated with a small proportion of SIDS cases then this leaves open the possibility that alpha-hemolysin could act on the heart through this pathway.

Prone sleep position

The discovery of the major risk factor of prone sleep position increased support for the cardiorespiratory hypothesis [39–41], and even led to declaration that prone position was involved in the causal mechanism, despite the knowledge that there were large numbers of deaths of supine and side-sleeping babies.

There has been a general lack of interest in possible mechanisms that could explain the prone position risk factor other than mechanistic ones invoking some sort of asphyxiation or a purported link to brainstem homeostatic malfunction. Plausible explanations (e.g. the influence of prone position on the nasopharyngeal flora in promoting colonisation with toxigenic bacteria [8], ingestion or inhalation of infective agents from the sleeping surface) have been proposed [42]. Published evidence that babies are at increased risk of SIDS if they sleep on a sofa [43] or sleep on a used (second-hand) mattress [44,45] or in a parental bed [46] seem to support this idea given the common finding of *Staphylococcus aureus* and *Escherichia coli* being associated with SIDS [47]. Both of these bacteria carry lethal toxins and are commonly found on the aforementioned contaminated sleeping surfaces involved. It would seem that the answer was overlooked by mainstream researchers. This oversight may have allowed SIDS research to meander onto less fruitful paths and could explain why, after decades of research, there still is no answer. This could be seen as unprecedented for scientific endeavour in the 21st century.

The epidemiological link

The key research that would have been helpful in understanding a more plausible role of prone sleep position as a risk factor for SIDS was contained in the data from the Tasmanian SIDS study [48]. The Nordic SIDS epidemiological study [49] provided supportive evidence. The salient data in these studies were seemingly overlooked by mainstream researchers. The Tasmanian study clearly indicated that risk of SIDS occurred in the prone position mainly when there was an accompanying illness defined as nasal congestion, cough, chest noises, fever, episodes of vomiting or diarrhoea on the day of death or previous day. These signs not unreasonably reflected either a respiratory or

gastrointestinal infection. “The prone position increased the risk of SIDS more than 10-fold among ill infants, but it was associated with only a slight increase in risk among well infants. This difference in risk was significant ($P = 0.02$)” [48]. The Nordic study [49], whilst primarily examining time of death, also showed increased risk of SIDS for prone-plus-infection but also showed that a cold in the last 24 h increased the risk of SIDS in supine/side sleepers. Interaction between infectious symptoms and modifiable risk factors including prone sleep position was shown in an earlier paper from the Nordic Epidemiological SIDS Study [50]. Smoke exposure, a known potentiator of acquisition and severity of viral infection (as well as enhanced viral adherence to epithelial cells) was also shown to be a significant contributor to SIDS pathogenesis in the abovementioned studies and numerous other studies [51,52].

It should be noted that the effects of prone position show extreme variability depending on age and other factors. Physiological studies have not examined whether (or not) infection alters physiological findings. It is therefore timely to remind physiology researchers of the role of infection in SIDS. Something important is happening when infection combines with prone sleep position, but discerning whether or not prone position affects physiological responses directly or that prone position is important in acquisition (through inhalation or ingestion) of infectious agents from a contaminated sleeping surface remains unanswered. Moreover, the increased SIDS risk of co-sleeping [53], of sleeping on a used mattress [45], or sofa [43], affords consideration of more likely exposure and acquisition of bacterial pathogens being the real underlying reason for these increased risks notwithstanding the effect of prone position on nasopharyngeal flora. Moreover, the frequent finding of *Escherichia coli* and/or *Staphylococcus aureus* in the lungs of SIDS/SUDI babies at autopsy provides additional supportive evidence [47]. This is explained by the work of Harrison et al. [54] which demonstrated the effect of prone sleep position on the nasopharyngeal bacterial flora. The consequences of such colonisation would likely increase the risk of bacteraemia and/or toxemia/sepsis in a susceptible baby at a vulnerable stage of development with predisposing SIDS risk factors. A question could be put that asks: why are the typical features of bacterial sepsis absent in SUDI/SIDS cases? To answer this, it must be noted that sepsis is difficult to diagnose in both life and death [4]. While FDPs are found to be elevated in SIDS babies [57], other markers of acute infection/inflammation (e.g. CRP, procalcitonin) are not elevated for they usually require a day or two to react. However, a fingerprint of raised proinflammatory cytokines (TNF- α , IL-6) are often found as mentioned previously.

Discussion

A previous article exposed weaknesses in the cardiorespiratory hypothesis of SIDS and demonstrated a lack of consistent correlation with clinicopathological and epidemiological data [3]. On the basis of the apparently missed increased risk of prone sleep position being directly associated with infection, it therefore behoves researchers to provide the necessary supportive evidence (currently lacking) from the CNS nuclei and receptor studies or to reconsider their whole approach bearing in mind that infection may trigger physiological dysfunction of brainstem and other nuclei through powerful immune mediators (e.g. prostaglandins, inflammatory cytokines, etc.). Mainstream research acknowledgement of the important findings in relation to the association between prone sleep position and infection is also awaited. Normally research evolves on the basis of new key information. Why mainstream research is not part of this evolution is surprising and hard to understand. It is also surprising that the CESDI SUDI studies [47] did not examine the prone/infection link. Forgetting history imperils.

Additional clues awaiting investigation include the fact that infection and lethal sepsis stimulates release of serotonin resulting in increased serum levels [55]; serotonin having been the focus of intense research but without apposite results [56]. The other clue relates to the universal finding of liquid, unclotted blood in the chambers of the

heart: sepsis causes thrombocytopenia which could be related to the heart blood findings. As mentioned, elevated FDPs is a feature of SIDS [58]. Raised FDPs occurs in infection and sepsis, with or without disseminated intravascular coagulopathy (DIC), however, DIC is not a feature of SIDS. Similarly, it is of considerable concern that the vasculopathy evidenced as petechial haemorrhages on/in intrathoracic organs in ~90% of SIDS cases [58,59] has not been investigated from an infection/sepsis viewpoint.

It is clear that “*diagnosis of sepsis as the cause of death can be difficult at autopsy, especially when a clear macroscopic or histological focus of infection cannot be identified*” [4]. This should be a lesson for future SIDS research because absence of findings does not mean absence of infection/sepsis. In explaining why normally sterile sites in a proportion of SIDS cases yields growth of *Staphylococcus aureus* and/or *Escherichia coli* [60,61] it is conceivable that these findings could represent a “footprint” of a lethal bacteraemic episode arising from lung infection with these bacteria [62]. Importantly, both of these pathogens are over-represented in cultures taken from the respiratory tract of SUDI/SIDS cases [63].

This article has highlighted the importance of the association between infection and the increased risk of SIDS when babies sleep prone. The reasons for this association have been reviewed and support the overarching congruence of infection with all SIDS epidemiological risk factors. The difficulty clearly is seen in obtaining proof of the infection hypothesis. Detailed inflammatory cytokine analysis would seem obligatory for every case of SUDI/SIDS. New technologies including “protein corona fingerprinting” seem to be able to separate sepsis from other inflammatory conditions including systemic immune response syndrome (SIRS) [64] and could be useful in analysing plasma from SIDS cases. m-RNA analysis in cases of SIDS is unlikely to be helpful owing to post-mortem effects. Perhaps the death scene examination should extend to environmental swabbing and culturing (at least the infant’s bedding) with bacterial nucleic acid sequencing studies for toxins. Broadening the approach by researchers examining the CNS to include infection/toxin exposure in any animal model could provide useful supportive information. The new science of proteomics (viral antigens, bacterial toxins, their degradation products, and the cytokine cascade) could also provide answers. Given this information, mainstream SIDS researchers are invited to review their hypotheses and consider fresh lines of research in line with the infection hypothesis.

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