Sudden infant death syndrome, virus infections and cytokines

Muhammad W. Raza*, C. Caroline Blackwell

Department of Medical Microbiology, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK

Received 15 October 1998; accepted 24 February 1999

Abstract

Many epidemiological risk factors identified for sudden infant death syndrome (SIDS) suggest a viral aetiology, e.g. exposure to cigarette smoke and winter peak, mild respiratory symptoms. Virus infections and bacterial toxins induce cytokine activity and it has been suggested that uncontrolled inflammatory mediators could be involved in some cases of SIDS. The aim of this review was to assess the evidence for virus infection in SIDS and to examine those findings in relation to individual variations in cytokine responses and various pathophysiological mechanisms proposed for SIDS such as sleep derangement, hypoxia, cardiac arrhythmia, vascular hypotonicity and hypoglycaemia. © 1999 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

Keywords: Virus infection; Cytokine; Sudden infant death syndrome; Sleep; Cardiac arrhythmia; Hypoxia; Apnea; Hypoglycemia; Circadian rhythm; Cortisol

1. Virus infections and sudden infant death syndrome (SIDS)

Extensive epidemiological studies in several countries have identified the major risk factors for SIDS. Many developmental and environmental factors significantly associated with these deaths parallel those associated with susceptibility of infants and young children to infectious agents, particularly infections of the respiratory tract. These include the age range affected, a winter peak of SIDS in many countries, exposure to cigarette smoke and poorer socioeconomic backgrounds. Case histories of SIDS infants often contain references to mild upper respiratory symptoms prior to death. Major signs of respiratory illness (wheezing, drowsiness, vomiting and bouts of coughing) in these infants during the 2 weeks before death were not significantly different from infants matched for age and sex who died from other causes. There were, however, significant differences in incidence of minor symptoms, snuffles and occasional cough, in these groups [1]. More deaths due to SIDS occur in winter months (Table 1) when virus infections are also prevalent [14–17]. Outbreaks of influenza A virus in children were significantly associated with SIDS, and the association was independent of effects of lower atmospheric temperature [18]. SIDS mostly affects the poor in prosperous countries [19–21] in whom infectious diseases are also relatively more common. Forsyth et al. [22] found higher levels of IgG and IgM, but not IgA, in the lungs at
necropsy of infants who died of SIDS compared with infants who died of non-respiratory causes.

While no single agent has been clearly identified as causing SIDS, many different viruses affecting both respiratory and gastrointestinal tracts have been identified in these infants [19] (Table 2). Exposure to cigarette smoke enhances susceptibility to respiratory virus infections [14], possibly by affecting various arms of the host defences against infection: non-specific immune responses [41]; humoral [42] and cellular immunity [43]; and macrophage functions [44]. Maternal cigarette smoking during pregnancy and passive exposure to cigarette smoke are significantly associated with SIDS [5,8,45–51]. Cigarette smoke might also alter pathophysiological sequelae of virus infections [52].

Early infancy (2–4 months), when most deaths from SIDS occur, coincides with a period of declining levels of maternal antibodies and immature immune responses in infants. Breast-feeding in many studies has been shown to be protective against SIDS [45,53,54]. The effect of breast-feeding in relation to SIDS was significant in infants of mothers who were non-smokers [55]. If infectious agents are involved in SIDS, the protection afforded by breast-feeding could be due to the anti-viral and anti-bacterial activities of secretory IgG and oligosaccharides present in human milk. Oligosaccharides in human milk have been shown to have antiviral activity [56–58].

While significant necropsy findings are essentially absent in SIDS, mild inflammatory changes are commonly reported [59]. Epidemiological and autopsy studies of SIDS or epidemiological studies of near-miss infants have provided evidence of virus infections (Table 2). Some negative reports on association between virus infections and SIDS might be attributed to early virus infection with symptoms not yet noticed or not taken as significant by the parents. Failure to isolate or detect viruses might be due to late or inappropriate microbiological sampling or lack of facilities to identify viruses. Newer molecular techniques have been used to screen for viruses, but they have not significantly increased the identification rate [29,31].

### 2. Cytokine levels in virus infections and SIDS

Various hypotheses to explain SIDS have been postulated. Negative findings at necropsy in infants who died of SIDS suggest a serious physiological derangement: hypoxia and apnoea; extreme alterations in body temperature; hypoglycaemia; hypoten-

---

**Table 1**

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinational</td>
<td>[2]</td>
</tr>
<tr>
<td>UK</td>
<td>[3–6]</td>
</tr>
<tr>
<td>France</td>
<td>[7]</td>
</tr>
<tr>
<td>New Zealand</td>
<td>[8]</td>
</tr>
<tr>
<td>Australia</td>
<td>[3]</td>
</tr>
<tr>
<td>USA</td>
<td>[9]</td>
</tr>
<tr>
<td>Sweden</td>
<td>[10,11]*</td>
</tr>
<tr>
<td>China</td>
<td>[12]</td>
</tr>
<tr>
<td>Japan</td>
<td>[13]</td>
</tr>
</tbody>
</table>

*No association was found.

**Table 2**

Reports on respiratory symptoms and virus isolates in cases of SIDS

<table>
<thead>
<tr>
<th></th>
<th>Associated with SIDS</th>
<th>Not associated with SIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory symptoms</td>
<td>[8,23,24]</td>
<td>[6,25]</td>
</tr>
<tr>
<td>Population mixing</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td>[18,27,28]</td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>[29,30]</td>
<td>[31]</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>[29,33–35]</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>[33]</td>
<td></td>
</tr>
<tr>
<td>Echovirus</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>Virus isolation</td>
<td>[36,37]</td>
<td>[1,27,38]</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>[34,39]</td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>[35,40]</td>
<td></td>
</tr>
</tbody>
</table>
sion; cardiac arrhythmia; or combinations of these factors. It has been suggested that in extreme cases interleukin 1 (IL-1), interferon (IFN) and tumour necrosis factor α (TNF-α) elicited by infections cause somnolence and hypoxia leading to death [60,61]. Blackwell et al. [62-64] suggested uncontrolled cytokine responses elicited by combinations of bacterial toxins, virus infection and/or cigarette smoke might precipitate a series of events leading to some of these unexplained deaths. Very high temperatures observed in some SIDS infants was thought to be the cause of death [65]; these extreme temperatures could have been induced by cytokines such as TNF-α and IL-1. A slight initial derangement of a few cytokines in response to an apparently trivial challenge is capable of triggering various cytokine cascades which might prove lethal. In septic shock, it is not the number of bacteria present but the body’s response to the bacteria that determines the severity of illness [66].

Viruses might cause minimal clinical symptoms in infants but trigger cytokine cascades culminating in sudden death. Bacterial pathogens or their products, cigarette smoke, or any combination of these might similarly amplify the production of proinflammatory cytokines. Whatever the identity of the agents, a final common pathway in the pathogenesis of SIDS is suggested by a combination of factors unique to SIDS: (1) a higher prevalence in the early hours of the morning; (2) an association with presumed sleep; (3) peak incidence of SIDS at 2–4 months; (4) and an absence of gross necropsy abnormalities.

Studies of cytokines in SIDS babies are scarce. Howat et al. [67] used cells obtained from the lungs to assess IL-4, IL-5 and IL-10. Significantly higher numbers of cells stained for the cytokines were found in SIDS babies compared with controls. Table 3 summarises studies of cytokines in virus infections for both in vivo and in vitro models.

3. Genetic factors: race and gender

The incidence of SIDS varies significantly between different ethnic groups [77,78]. In Britain, the incidence of SIDS among Indian, Pakistani and Bangladeshi families is lower than in the white population. Infant deaths due to respiratory infections are also lower than in white families [79]. Although low socioeconomic standards have been significantly associated with SIDS in Britain [80], in Hong Kong, where many families live in suboptimal circumstances, there is also a very low incidence of SIDS [81].

On the other hand, some indigenous populations have high incidences of SIDS, e.g., American Indians, Alaskan natives and Australian Aborigines [82,83]. The criticism that the higher incidence of SIDS in the Aboriginal infants was due to differences in diagnosis was addressed by re-examination of all Aboriginal cases of SIDS and sudden unexpected death in infancy between 1980 and 1988 and a corresponding random sample of non-Aboriginal cases. There was no evidence of differences in diagnosis of SIDS in the two populations [84]. Among Native
Americans, Eskimos and Australian Aborigines, the incidence of serious respiratory tract and ear infections is also higher [85,86].

Environmental and cultural factors are thought to contribute to some of these differences. Epidemiological studies indicate that in groups in which smoking is less prevalent among women, deaths due to SIDS are lower. Studies on American Indians and Alaskan natives examined the prevalence of risk factors on populations in which there was a significant difference in incidence of SIDS. From 1984 to 1986 the incidence of SIDS was 4.6 per 1000 live births among Indians and Alaskan natives in the northern region of the USA. In contrast, the incidence among southwestern Indians was 1.4 per 1000 live births. There was no significant difference between the incidence of SIDS in white populations in the two regions with 2.1 and 1.6 per 1000 live births in the north and southwest regions respectively. Socioeconomic status, maternal age, birth weight or prenatal care were not significantly different among the Indian populations in the two areas. The prevalence of maternal smoking during pregnancy was exceptionally high among northern Indians and Alaskan natives but low among the Southwest Indians [82].

In Britain smoking is more prevalent among lower socioeconomic groups [87], and both smoking and poorer socioeconomic conditions were found to be significant risk factors for SIDS [51,80]. Among Asian women of all social classes, smoking is very rare [77], and we have suggested that this might contribute to the lower levels of both SIDS and respiratory deaths in these populations. This could be related to reduced frequency or density of colonisation by potential pathogens or to a lower level of absorption of water-soluble components of cigarette smoke that could enhance inflammatory responses to infection.

Polymorphism in individual susceptibility to infections is expected. Immune responses and proinflammatory cytokines have been reported to differ in several ethnic groups. In white subjects, a TNF2 variant at locus TNF-308 was shown to be significantly associated with HLA-DR3, which also showed a strong association with white subjects compared with black populations [88]. Important ethnic differences were found in the genotype of TNF-α and its linking to MHC alleles [89].

There appears to be a significant genetic component associated with induction of both pro-inflammatory (TNF-α) and anti-inflammatory (IL-10) cytokines [90,91]. Fatal outcome of meningococcal disease was significantly associated with low TNF-α responses and/or high IL-10 responses of first-degree relatives of the patient [91]. Studies on differences in pro- and anti-inflammatory responses to virus infections have not been carried out in different ethnic groups.

SIDS affects more male than female infants [7,49,83]. RSV infection was more common in hospitalised male infants; the ratio of males to females was 1.44:1 [92]. Compared with female infants, significantly more males suffered with RSV, influenza and parainfluenza viruses, rhinovirus and adenovirus [93].

4. SIDS and sleep

Sleep is physiologically very different from wakefulness. Higher neuronal disinhibition in sleep is associated with changes in cardiovascular and respiratory systems, as witnessed in adult sleep apnoea syndrome. Most SIDS cases have been reported in infants during presumed sleep in the early hours of the morning [94]. IL-1, TNF-α and IFN-γ have been shown to be somnogenic in physiological conditions and during infections [95]. Since hypoxia has been proposed as a possible cause of SIDS, the effects of virus infections and cytokines on hypoxia are reviewed below (Section 8).

Circadian rhythm can affect the numbers of immune cells in circulation. Compared with wakefulness, there was an acute reduction of the number of natural killer cells, monocytes and all subsets of lymphocytes during nocturnal sleep in healthy men [96].

5. Cytokines, cortisol and circadian rhythm

Circadian rhythm is a characteristic of neuroendocrine pathways. Two important neuroendocrine hormones, cortisol and melatonin, were suggested to affect diurnal variations in the levels of IFN-γ and IL-10 observed with an in vitro model in which
whole blood was challenged with bacterial LPS or tetanus toxoid. INF-γ was highest and IL-10 was lowest during the early morning hours and correlated negatively with plasma cortisol and positively with melatonin [97]. Urinary free cortisol levels in subjects between 1.8 and 17 years were found to be positively correlated with age [98]. Impairment in the ability to control inflammatory mediators resulting from low night-time cortisol levels associated with changes accompanying development of adult-type night-time temperature rhythm was proposed as a ‘window of vulnerability’ to SIDS [63]. Viral infections might hinder cortisol release from the adrenals in response to stimulation by corticotrophin releasing hormone (CRH) from the pituitary gland. Stimulation by CRH resulted in a reduced or a blunted cortisol response in some men with HIV infection [99].

Sleep was associated with enhanced production of IL-2 by CD3+ T cells but not of IL-1, TNF-α or IL-6, and the effects were independent of cortisol levels [96,100]. Uthgenannt et al. [101] found similar effects of sleep on IL-2 production. Monocytes from subjects obtained during nocturnal sleep were stimulated in vitro by LPS from Escherichia coli; they showed significantly higher TNF-α and IL-1β compared with monocytes obtained when the subjects were awake. Association of cytokines and sleep was further substantiated in patients with obstructive sleep apnoea syndrome. These patients experience disturbed sleep patterns, less sleep at night and spells of sleep during the day. Nocturnal peaks of TNF-α disappeared in these patients and a daytime peak had developed [102]. Cortisol was shown to have damping effect on the somnogenic cytokines, IL-1, IL-2, TNF-α and IFN. While cortisol is induced by virus infections, its production in response to virus infections is not as efficient compared with the response to bacterial infections [98].

6. Infections, cytokines and sleep regulation

Sleep, like fever, is a common manifestation of infection. Most deaths attributed to SIDS occur during presumed sleep between midnight and 8.00 a.m. when many somnogenic cytokines (IL-1, IL-2, IL-6, TNF-α, and IFN) are at a peak. Human recombinant TNF-α and IL-1 were shown to cause or prolong slow-wave sleep and suppress the rapid eye movement (REM) phase of sleep [103,104]. Similar effects were observed in rabbits with human recombinant IFN [105]. Immunisation and strain difference in mice were associated with dissimilar sleep pattern after challenge with influenza virus; some mice had deeper, more prolonged sleep than others [106].

Virus-associated double-stranded RNA extracted from mice infected with influenza virus and a synthetic double-stranded RNA were shown to cause flu-like symptoms and non-REM sleep in rabbits [107]. Serum anti-viral activity, probably due to IFN, was associated with sleep [107,108]. Bacteria and their products have similar somnogenic effects [109,110].

7. Hypoxia, reflex apnoea and SIDS

Airway obstructions, other than suffocation, leading to chronic and acute hypoxia have been postulated as a cause of death in SIDS infants. Profound hypoxia and infection were necessary experimental conditions to produce intrathoracic petechiae in rats, a characteristic of the autopsy changes observed in SIDS infants [59]. Levels of cortisol in infants who died of SIDS without petechiae (9 μg per 100 ml) were lower than that of SIDS infants showing intrathoracic petechiae at necropsy (25 μg per 100 ml). SIDS infants with petechiae also showed 20% more muscle mass in pulmonary arteries compared SIDS infants without petechiae, indicating the existence of chronic hypoxia/hypoventilation in the first group [59]. Rognum and Saugstad [111] suggested tissue hypoxia was a cause of death from comparison of hypoxanthine levels in vitreous humor from SIDS and comparison groups included in their study. Multiple brief apnoeic attacks were noticed in infants who eventually died of SIDS [112]. Some workers have, however, argued against hypoxia as a possible cause of SIDS [113,114].

8. Effects of virus infections and cytokines on hypoxia and reflex apnoea

Reinforced reflex apnoea was observed in infants
with infection due to RSV compared with uninfected infants [115], and this was suggested to be one of the mechanisms of sudden death in some infants who suffered mild respiratory symptoms before death [116]. Apnoeic attacks can cause near-miss SIDS in infants with RSV infection [117].

9. Cytokines and regulation of vascular smooth muscle cell contractility and vascular tone

Proinflammatory cytokines (TNF-α, IL-1, IFN-γ) released in response to viral infections modulate vascular contractility primarily through regulation of nitric oxide (NO), a potent vasodilatory factor [118]. Vascular endothelial NO production is constitutively controlled and modulated by bradykinin, acetylcholine and epinephrine. Baseline vascular tone is maintained in partial relaxation due to NO [118,119]. Vascular smooth muscle cells can also release vast amounts of NO when stimulated by the proinflammatory cytokines [120].

10. Cardiac arrhythmia, SIDS and cytokines

Gunteroth reviewed studies on SIDS relating to possible cardiac causes of death and concluded a
cardiac theory of SIDS was not sustainable [121]. There is, however, some evidence that arrhythmia without structural cardiac abnormalities might cause sudden death in SIDS. REM sleep is a vulnerable phase for cardiac arrhythmia [113]. Abnormally increased heart rates during sleep were reported in subsequent siblings of SIDS infants [122] and near-miss infants [123]. Long QT syndrome is characterised by ventricular fibrillation and, sometimes, fatal syncopal attacks [124]. Long QT interval was considered to be an important risk factor for SIDS in a prospective study of a large group of infants [125]. Arrhythmia has been reported as a side effect of treatment of patients with metastatic cancer with TNF, IL-2 and IFN-\(\gamma\) [126,127]. Negative ionotropic and arrhythmogenic effects were observed in myocytes cultured in IL-1, IL-2, IL-3 and TNF-\(\alpha\) [128].

11. Hypoglycaemia and cytokines

Acute hypoglycaemia has been associated with deranged cytokine levels. Hypoglycaemia was induced in rats with TNF-\(\alpha\) without changes in the insulin levels; it was ameliorated with corticosteroid therapy [129]. Hypoglycaemia in an elderly patient with non-Hodgkin’s lymphoma was associated with normal insulin and insulin-like hormone levels but with high TNF-\(\alpha\) levels. It was normalised after correcting TNF-\(\alpha\) by cytoreductive therapy [130]. TNF-\(\alpha\)-like molecules might be responsible for hypoglycaemia observed in cerebral malaria [131]. Staphylococcal enterotoxin B caused weight loss and hypoglycaemia in rats. This was prevented by antibodies against IFN-\(\gamma\); levels of TNF-\(\alpha\) and IL-6 remained unchanged [132].

12. Conclusion

Animal models indicate that the inflammatory response to viral infections could have a priming effect via INF for induction of high levels of mediators such as TNF-\(\alpha\) or nitric oxide [133]. We proposed the hypothesis that virus infection, alone or in conjunction with bacteria, their toxins or cigarette smoke, might induce an uncontrolled cytokine cascade which could contribute to the events leading to sudden deaths in infants. Virus infection has been demonstrated to enhance bacterial binding to epithelial cells in vitro [134–136]. Compared with infants with no signs of respiratory infection, infants with respiratory viral infections have significantly more bacteria and more species of bacteria in their nasal secretions when sleeping in the prone position; and, the species of bacteria are similar to those isolated from SIDS infants at autopsy [137]. Fever, prone sleeping and blocking of nasal passages with secretions could induce a micro-environment in which the permissive temperature for induction of potent bacterial toxins is obtained. Virus infections have been demonstrated to enhance the lethality of bacterial toxins in animal models [138] and to enhance induction of inflammatory mediators from human cells in vitro [139,140].

Physiological systems regulating cytokines, sleep and body temperature are closely interrelated. Infants develop circadian rhythm during the age range in which most SIDS cases occur. During the period following the switch to adult-like temperature rhythms, the physiological changes that occur in endocrine responses and hormone levels might result in infants producing lethal amounts of proinflammatory cytokines in response to infectious agents and/or exposure to cigarette smoke. The uncontrolled production of these cytokines could affect any of the mechanisms proposed as possible causes for SIDS [133] (Fig. 1).

Acknowledgements

This work was supported by grants from Chest, Heart and Stroke, Scotland and The Scottish Cot Death Trust.

References


