Paediatric Respiratory Reviews 15 (2014) 307–311

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Sudden Infant Death Syndrome

Infectious causes of sudden infant death syndrome

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EDUCATIONAL AIMS:

To summarise the current literature on infectious aetiologies of SIDS by looking at viral, bacterial, genetic and environmental factors which are believed to be associated with SIDS.

The reader will come to appreciate that:

- There is inconsistency in the definition of SIDS cases.
- Winter peaks have been consistently reported in series of SIDS patients which raise the possibility of an infectious aetiology in SIDS.
- Bacteria such as Staphylococcus aureus are more often reported in SIDS cases.
- Superantigens and toxins may play a role in SIDS cases.

ARTICLE INFO

Article history:
Received 15 September 2014
Accepted 15 September 2014

Keywords:
Sudden infant death syndrome [SIDS]
Sudden unexpected death in infancy [SUDI]
Aetiology
Infection

SUMMARY

Investigators have long suspected the role of infection in sudden infant death syndrome (SIDS). Evidence of infectious associations with SIDS is accentuated through the presence of markers of infection and inflammation on autopsy of SIDS infants and isolates of some bacteria and viruses. Several observational studies have looked into the relation between seasonality and incidence of SIDS, which often showed a winter peak. These all may suggest an infectious aetiology of SIDS. In this review we have summarised the current literature on infectious aetiologies of SIDS by looking at viral, bacterial, genetic and environmental factors which are believed to be associated with SIDS.

INTRODUCTION

Sudden infant death syndrome (SIDS) is the sudden death of an infant aged less than one year, which remains unexplained after a thorough investigation including complete autopsy, examination of the death scene, and review of the clinical history [1–8]. SIDS cases form a subset of sudden unexpected death in infancy (SUDI), which is any infant death that is unexpected and initially unexplained [9]. Most of the time, a cause of death is determined after thorough investigation and autopsy. However, those deaths that remain unexplained after through investigations are defined as SIDS; a diagnosis of exclusion and its validity depends upon the accuracy and completeness of the investigations [9].

Although SIDS rates have declined worldwide over the last 20 years, it is considered as the leading cause of death for infants aged 1 to 12 months in developed countries [10]. Several factors have been identified that may increase a baby's risk of SIDS including male sex, prone sleeping, exposure to cigarette smoke, young age, ethnicity, family history of SIDS and prematurity [11–14]. Moreover, investigators have long suspected a role for infection in SIDS [13]. One of the first studies investigating the role of infection in SIDS, published in 1961, looked at viral aetiologies of SUDI. Where among 48 infants with sudden, unexpected death the investigators detected a viral agent in 12 (25%) [15].

The hypothesis suggesting an infectious origin of SIDS is supported by the presence of markers of infection and inflammation on autopsy, and isolates of specific bacteria and viruses [16–21]. Microorganisms

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http://dx.doi.org/10.1016/j.prrv.2014.09.004
1526-0542/

may increase inflammation either as super-antigens or via endotoxins in their cell wall. Several studies have shown that *Escherichia coli (E. coli*) is more likely to be found in post-mortem examination of SIDS infants compared with infants who died from proven non-infectious causes [22,23]. It is also thought that an irregular response to an infectious insult could act as a trigger for SIDS in some cases [24]. Whilst a comprehensive and universally accepted explanation for SIDS is still a long way away, several important risk factors have already been identified which includes infection [25].

SIDS AND INFECTIOUS AETIOLOGY

There is increasing evidence to suggest that infections may play an import role in SIDS either by direct invasion and/or by bacterial toxins associated with abnormal host response [26]. Several ecological studies (population studies of seasonal exposure to infections) have examined the relationships between seasonality and incidence of SIDS, which often show a winter peak [27]. This would be consistent with a contribution from respiratory viruses.

Autopsies on cases of SIDS showed increased isolation of staphylococci and Gram-negative bacilli compared with matched healthy controls [28]. Some studies showed that Staphylococcal toxins and endotoxins were present in SIDS tissues but antibodies to endotoxins were low, leading to the common bacterial "toxin hypothesis" [29]. Bacterial toxins derived from upper airway organisms are present in young infants, when maternal IgG concentrations declines prior to maturity of the infants' immune system. Some toxins may act as super antigens resulting in a massive release of pro-inflammatory cytokines which could lead to toxic shock-like syndrome or septic shock and death [11,29]. The age distribution of SIDS also support this hypothesis, as the incidence of SIDS rises rapidly from birth to a peak at 8–10 weeks of age and then falls. SIDS deaths are uncommon after 6 months of age [29,30]. This age distribution is consistent with the immunoglobulin concentration profiles that protect against infections by bacteria and toxins [29]. Moreover, prone sleeping position leads to pooling of secretions in the upper respiratory tract which eventually increases bacterial growth and toxin production [29].

VIRAL INFECTION AND SIDS

The epidemiological features of SIDS strongly suggests that viruses, either directly or indirectly through synergistic interactions with bacterial virulence factors and/or immunoregulatory polymorphisms, may have a significant role in SIDS by enhancing the lethality of the bacterial toxins [11,31]. The existence of viruses in the respiratory tract of an infant can alter sub-lethal doses of bacterial toxins to lethal doses [13]. However, the mechanisms behind this are not yet fully understood [32].

Respiratory viral infections fits the infectious hypothesis well as the most likely trigger for SIDS. [13]Studies have found that a viral mild upper respiratory tract infection is often seen in nearly 80% of SIDS cases few days preceding death [13,33]. Moreover, several studies have shown higher rates of respiratory viruses isolated from SIDS cases when compared with controls (Table 1). However, to date no single respiratory pathogen has been found to be causally related to SIDS. [13] Despite divergent study conclusions, the association between viral infection and the pathogenesis of SIDS is strengthened by the epidemiological and pathological evidence [13.]

TOXIGENIC BACTERIA AND SIDS

Studies suggest that in some cases of SIDS nasopharyngeal bacterial toxins may trigger events that may lead to an infant's death. One large observational study by Blackwell *et al* [28] attempted to explore which species fitted with the bacterial toxin hypothesis by assessing the nasopharyngeal flora of healthy infants in relation to risk factors. That study showed that in healthy infants $\leq$3 months of age, *Staphylococcus aureus* (*S. aureus*) was isolated in 57% compared with 86% for SIDS infants in that age range ($P<0.02$). *S. aureus* fitted with the mathematical model for SIDS, and staphylococci with their toxins were identified in a relatively significant proportion of SIDS cases [28].

Numerous studies examined the association of *E. coli* with SIDS. *E. coli* colonises the bowel of infants in first few days of their life and several studies have isolated *E. coli* from SIDS cases [19]. However, serotypes of *E. coli* that were found in the intestinal tract of SIDS infants are typically extra-intestinal [13]. Out of various toxins of *E. coli*, heat stable enterotoxin (ST), heat labile enterotoxin (LT) or verocytotoxin (VT) are accountable for toxigenicity of *E. coli*. These toxins have been well studied [13] Therefore, other unidentified or less studied toxins could be associated with these toxins and may share a transmission vector (i.e. bacteriophage). [19]

Table 1
Studies exploring the role viral infection in SIDS

Study	Country	Sample size	Infective Aetiology
Burger *et al* 2014 [9]	South Africa	82 SUDI cases	PCR positive Cytomegalovirus in 29 (35%) and Adenovirus in 2 (2%) cases
Desmons *et al* 2013 [48]	France	2 month old male infant 8 days after the onset of benign varicella	Cytomegalovirus and varicella zoster virus were detected by molecular biology
Schuffenecker *et al* 2012 [49]	France	1128 CSF specimen examined for human parechovirus type 3 (HPeV-3)	One case of SIDS (11-day-old girl who died from SIDS positive for HPeV-3)
Drexler *et al* 2011 [50]	Germany	10 myocardium specimens in infants who died of SIDS	1 positive for human cardioviruses (hCV genotype 2)
Niklasson *et al* 2009 [51]	Sweden	8 SIDS cases (5 SIDS and 3 SIDS Myocarditis)	Ljungan virus positive in 7 cases (6 from CNS specimen, 3 positive in heart specimen, 3 in lung specimen)
Krous *et al* 2009 [52]	USA	24 SIDS cases	NO PCR detected adenovirus or enterovirus. Symptoms of URI within 48 hours of death in 7/17 cases
Alvarez-Lafuente *et al* 2008 [53]	Spain	11 cases and 9 controls	DNA prevalence of Herpes viruses (CMV, EBV and HHV-6) 72.7% (8/11), in cases (i.e. SIDS) vs. 22.2% (2/9) in controls (p = 0.025).
Dettmeyer *et al* 2004 [54]	Germany	62 SIDS cases and 11 controls with unnatural death.	Enteroviruses 22.5%, Parvovirus B19 11.2%, Epstein-Barr viruses 4.8%, Adenoviruses 3.2% and human herpes simplex virus type 6 (HHSV6) 1.6% in SIDS groups vs. no virus detected in controls
Kashiwagi *et al* 2004 [55]	Japan	16 months child	Parainfluenza virus type 2 was cultured in the nasopharynx and detected by PCR in liver tissue and bone marrow