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Research Article

SIDS Risk Factors: Time for New Interpretations. The Role of Bacteria

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Abstract

The aim of this paper is to help draw attention to perceived ideas regarding the risk factors and the implied pathogenesis of Sudden Infant Death Syndrome (SIDS), and SIDS research in general. Our paper shows there is little if any evidence to support the broadly held notion of an association between respiratory function and sudden infant death syndrome. Researchers who hold to this approach to explain the risk factors of bed-sharing and prone sleep position, etc. have failed to meet the standards of scientific endeavour that we would expect of good research. To counter this imbalance we have proposed an evidence-based explanation for SIDS risk factors showing that microbiological studies of SIDS corroborate epidemiologic and pathological data in establishing a plausible pathogenetic mechanism. We reviewed recent publications on current research and the epidemiology of SIDS and publications on the microbiology of SIDS. Conclusion: Comparison of the data presented, suggest that the risk factors of bed-sharing, and smoke exposure, prone sleep position and alcohol can be explained by the theories of a microbiological infection model of SIDS pathogenesis.

Keywords: Sudden Infant Death Syndrome, bacteria, infection, risk factors.

Introduction

The Problem

Important papers such as the recently published one by Mitchell *et al* (2012) continue to present the risk factors of prone sleep position and bed-sharing in a way that infers respiratory compromise. Similarly, recent studies into these SIDS risk factors would appear to take the same "respiratory" approach to the problem (Baddock et al. 2012). Therefore, it is timely to re-examine and expose this persistent and costly pursuit by SIDS researchers to conduct studies into respiratory physiology when it is clear that any relationship of this approach to SIDS is somewhat tenuous and does not fit with the most plausible physiological events that take place during a SIDS death (Poets 1996, Poets et al. 1999) In their paper Baddock *et al* (2004) state "Desaturation events to <90% were seen more often in bed-sharing

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(BS) infants than in cot-sleeping (CS) infants, although the importance of this event as a risk factor for SIDS is unclear. Episodic apnea (Hoppenbrouwers et al 1980) and periodic breathing (Horemuzova et al 2000) occur in normal infants and are not observed more frequently in future SIDS victims (Franco et al 1999)." While we recognize the role of intercurrent or subclinical respiratory infection (Hoffman et al 1988) in SIDS pathogenesis, [such as that caused by viruses or possibly *Pneumocystis* jerovecii (Vargas et al 2013) plus the histopathological evidence of platelet aggregation with signs of inflammation with capillary thrombosis, resulting in ischaemia (Hanssen & Jørgensen 2010)], we consider it is disingenuous to continue lines of research that infer an underlying respiratory compromise based on apnea, central control of breathing and/or asphyxia: we state this for the following reasons based on the following key areas of evidence. Our argument does not contradict nor exclude the multi-factorial basis of SIDS as proposed in the triple risk model (Filliano and Kinney, 1994) in which several host and environmental factors conspire to result in SIDS. Our argument will show that infection holds a key position in these events.

1) Brainstem Changes, Smoke Exposure: Arousal Inhibition or Cardiogenic Effect?

Children who died of SIDS tend to have higher concentrations of nicotine in their lungs than control children, regardless of whether smoking was reported. (McMartin et al., 2002). Similarly cotinine levels in pericardial fluid used as an indicator of exposure to cigarettes were higher in SIDS than controls (Milerad et al 1998). These studies provided direct support of the relationship between environmental tobacco smoke and the risk of SIDS. While prenatal nicotine exposure can permanently alter lung development and airway function (Sandberg et al 2004) it can have other effects on the developing fetus that could be more important in terms of relationship to the development of SIDS. The importance of prenatal nicotine exposure in terms of its effect on lung development, may be overridden by postnatal nicotine exposure on other critical physiological pathways given its causal linkage to SIDS (Cohen et al., 2002). Nicotine significantly reduced breathing drives in a sleeping mouse model, this could exacerbate hypoxia. However, effects on arousal were less certain and therefore failure of arousal may not be part of the SIDS picture. Other effects of nicotine which could be more important in relation to SIDS include its effect on cardiac vagal neurons (CVNs) in the brainstem (Huang et al. 2005). In animals exposed to nicotine in the prenatal period, hypoxia/hypercapnia recruited an excitatory neurotransmission to CVNs. The study established a likely neurochemical mechanism for the exaggerated decrease in heart rate in response to hypoxia/ hypercapnia observed in SIDS cases.

Translating animal lung mal-development subsequent to prenatal nicotine exposure to the human infant is not easily made as there is little if any anatomical evidence to indicate that nicotine causes abnormal prenatal lung mal-development in victims of SIDS *per se*. Certainly we are aware of the influence of maternal smoking on shortening gestation. Hence poor lung development in this context is a given. While prenatally-smoke-exposed infants may have tidal and forced expiratory flow rates reduced, suggesting that small airway development could have been affected (Lodrup Carlsen et al. 1997; Stocks et al. 2003), anatomical evidence in SIDS cases is wanting.

Given that not all SIDS babies have been exposed to nicotine pre- or post-natally, then lung mal-development is not a *sine qua non* for the eventuality of SIDS. On the other hand, brainstem effects (as described above and henceforth in the context of cigarette smoke exposure) are likely to be more important especially if one considers serotonin hyper-innervation which is claimed to be a hallmark of SIDS, and the hyperactivity in this regard could also account for the down-regulation of

serotonin receptors (Slotkin et al. 2011). Deficient cardiac sympathetic innervation is also consistent with increased vulnerability to hypoxia in the terminal stages of SIDS. Slotkin et al. (2011) showed nicotine exposure in a primate model produced brainstem and autonomic abnormalities of key monoamine systems that contribute to the response to hypoxia. According to Machaalani et al (2011) nicotine influences SIDS risk through effects on nicotinic acetylcholine receptors (nAChRs) in brainstem nuclei that control respiration and arousal. Neuronal apoptosis caused by nicotine could lead to loss of cardiorespiratory reflexes, compromising the infant's ability to respond to stressors such as hypoxia (Bejjani et al. 2013). Most SIDS deaths appear to occur during sleep which has concentrated interest in arousal and its purported failure. Given that babies of 3-4 months of age spend much of their life asleep it would be an understandable mistake to put too much weight on failure of arousal as the underlying mechanism in SIDS. Indeed SIDS that have occurred in fully awake babies (Krous et al. 2008) seems to demolish the arousal-failure hypothesis. Whereas, if due consideration is given to cardiogenic effects (supported by good evidence of profound bradycardia) and hypoxaemia and the precipitants thereof (i.e. infection), much more progress in our understanding of SIDS pathogenesis would have been made by now.

Proponents of the "respiratory SIDS model" quote such studies as that of Lindgren et al. (1996). While it has been shown that respiratory responses are affected in animal models with an underlying viral infection (Lindgren et al.1996), it is a long stretch to use this as evidence of a respiratory component in SIDS especially when the model involved respiratory syncytial virus (RSV)-infected (showing bronchiolitis and pneumonitis) and -uninfected 3-5 day-old lambs whose responses to laryngeal stimulation (with water) had been compared. Failure to arouse and to terminate reflex apnea in a minority of infected lambs was used as evidence of a role in the pathogenesis of respiratory tract infection-associated SIDS. Other studies using the much more direct approach of observation of mucosa-associated lymphoid tissue (MALT) in the respiratory tract of SIDS and non-SIDS deaths failed to show differences indicating there is probably no specific fundamental respiratory aspect to mucosal immunological responses to infection in SIDS. (Debertin et al. 2006).

2) Memory Monitored SIDS Cases: The concise review by Poets (1996) presents evidence against an association between apnoea and SIDS and is based on objective recordings of pathophysiological events immediately preceding SID. Fourteen such recordings have been published. Poets et al (1999), Poets et al (1993), Byard & Krous (2001), Haas et al (1993), Hilton (1998), Kelly et al (1991), Meny et al (1994), Poets & Southall (1993), Baird (2004). Poets et al (1999) concluded that none of the recordings showed evidence of prolonged central apnoea having occurred or being the primary cause of death. The primary event in every case was shown to be probable hypoxaemia followed by progressive bradycardia which developed over minutes or hours. The exact cause(s) of the heart slowing could not be ascertained, but was considered to be due to hypoxic cardiac depression (Poets et al 1993, Poets & Southall 1993, Baird 2004, Bentele & Albani 2008). The hypoxaemia seemed to be a necessary contributor to the cardiac events.

No studies support a role for idiopathic acute life-threatening events (ALTEs) in SIDS pathogenesis, nor are these the result of the same mechanism. (Poets et al 1993, Farrell et al 2002) Fewer than 10% of SIDS victims have a history of a prior ALTE as shown in the huge multicenter Collaborative Home Infant Monitoring Evaluation (CHIME) study (Ramanathan et al 2001). The findings of this study of 1,079 infants and 718,358 hours of monitoring demonstrated that both conventional apnoea and bradycardia and extreme apnoea and bradycardia are relatively common events, even among healthy term

infants. Preterm infants including up to 43 weeks' post-conceptional age were the only group that had an increased risk of such events compared with healthy term infants. Notably the peak incidence of SIDS is more than that for preterm infants of any gestational age. Therefore, the evidence shows that prolonged apnoea and bradycardia are not immediate precursors of SIDS. Thus, the CHIME study could not determine if infants who had episodes of extreme apnoea or bradycardia were at higher risk for SIDS, nor could it determine whether or not home monitoring could provide warning in time for intervention. Furthermore, the study could not provide evidence that intervention would prevent unexpected death. Other epidemiologic studies have failed to document any impact of home monitoring on the incidence of SIDS. It can be concluded that home monitoring has no impact on ***prevention of SIDS.*** Nevertheless, despite the lack of correlation between SIDS and ALTE, many of the risk factors found in SIDS infants are shared with those in ALTE infants (Ramanathan et al. 2001) and these possibly relate to immune dysregulation which could indicate that both conditions share parts of a pathogenetic pathway (Gleeson et al 2004).

2) The "Heart" of SIDS Pathogenesis

Many clues indicate the heart (under conditions of hypoxaemia) could be the final link in the SIDS story. The work of Sartiani et al (2010) could provide answers to the link between smoking in pregnancy, and fetal exposure to carbon monoxide and abnormal cardiac development, given that SIDS babies' hearts show developmental abnormalities (Naeye et al 1976). A study of 33,034 infants found that 50% of infants who died of SIDS had a prolonged QT interval in the first week of life (Schwartz et al 1998). About 10 percent of SIDS babies carry genetic variants in sodium and potassium channels that may cause prolonged QTc, (Arnestad et al 2007) or variants in the gap junction protein Connexin43 (Cx43) (Van Norstrand et al 2012). This indicates there could be a role for abnormal electrical conduction in SIDS, but the underlying cause(s) in the vast majority of cases remains unexplained. While prolonged QT is estimated to occur in 10 percent of SIDS cases, so it is difficult to explain the shortfall unless one invokes an underlying cardiac developmental abnormality. One hypothesis implicates hypoxia adversely influencing cardiac development in early life. Using non-invasive electrocardiogram (ECG) recording in mice Neary *et al* (2013) catalogued ECG changes from birth to 10 postnatal days, measuring changes in heart rate, QTc interval and QRS duration. By altering ambient oxygen concentration or genetically manipulating cellular hypoxic signalling in neonatal mice, the authors showed that an increase in ambient oxygen concentration after birth was important for driving maturation of cardiac electrical conduction. Reduced oxygen predisposed mice to arrhythmia and sudden death, which was associated with ECG abnormalities. At the cellular level, reduced oxygen caused aberrant gap junction phosphorylation and distribution, and misexpression of cardiac ion channels. The findings were congruent with known SIDS risk factors including respiratory infections, central nervous system abnormalities and prone sleeping position. Applying these constructs to human babies in terms of cause and effect is not entirely straightforward. A combination of underlying genetic and developmental abnormalities quite separate from a proposed chronic hypoxic environment would suffice to predispose the infant to an arrhythmia brought on by an acute or subacute hypoxaemic event precipitated by infection. This would seem more plausible. Moreover, there is evidence of subtle pathological changes indicating probable viral myocarditis in SIDS babies (which could contribute to SUD) (Rambaud et al., 1992; Young 1992; Dettmeyer et al. 2004). Dettmeyer et al. (2004) showed the importance of viral myocarditis in SIDS by demonstrating the presence of nucleic acid of enteroviruses, adenoviruses, Epstein-Barr virus (EBV) and parvovirus B19 in SIDS heart tissue but not in controls. Bajanowski et al (2003) showed histopathological and PCR evidence of viral

myocarditis. In another study influenza A&B, parainfluenza virus 3, respiratory syncytial virus were found in association with interstitial pneumonia more frequently in SIDS than controls. The authors (Bajanowski et al 2003) concluded that the association between interstitial pneumonia and some viruses supports the hypothesis that respiratory virus infections could act as a trigger in sudden infant death. Virus infection in SIDS is common but does not necessarily explain SUD. Apart from the obvious cardio-lethal effect of viral myocarditis, the essence of the role of viruses might be seen in relation to co-incident bacterial infection. This work indicated that a combination of a sub-lethal viral infection with a sub-lethal bacterial infection could produce a lethal outcome. Viruses profoundly augment bacterial toxin lethality (Jakeman et al 1991) as does cigarette smoke exposure. Not only is there virus-bacteria interaction, but toxins of different bacteria (e.g. *S. aureus, E. coli*) act synergistically and lethally. (Sayers et al. 1995).

3) Prone Sleep Position and Respiratory Obstruction

Upper respiratory obstruction due to purported anatomical changes when the baby is placed prone has been the basis of Tonkin's (Tonkin et al 2002) and Krous' (Krous et al 1984) groups approach to SIDS. Little supportive evidence exists (Stephens et al 2010). The hypothesis is flawed because the proposed mechanism is inherently undermined by the lack of evidence that asphyxiation is a plausible mode of death in SIDS (Poets 1996).

A variety of mechanisms that come under the heading of asphyxia have been expounded in the literature; these include smothering/overlaying and co-sleeping, obstruction of breathing by soft bedding/coverings, and central apnea. The apparent popularity of these seems to be founded on a possible link with the important prone sleep position risk factor. In comparison to supine, the prone position reduces autonomic activity through decreased parasympathetic activity and promotes sleep and raises arousal and wakening thresholds. In preterm infants resting ventilation and ventilatory drive is improved, but older infants (>1 - 3 months), show no improvement in ventilation. The prone position is associated with poorer ventilatory drive (in active sleep only). The majority of findings suggest a reduction in physiological control related to respiratory, cardiovascular and autonomic control mechanisms, including arousal during sleep which is reduced in the prone position. Careful interpretation is required as conclusions are derived from studies of healthy infants (Galland et al 2002). There are other factors that contribute to the prone risk factor: prone sleeping infants were shown to be more likely to be formula fed and exposed to passive smoking than control babies (and hence this association suggests additional risk factors for SIDS are also at play) (Lindgren et al. 1998). A more plausible explanation of why prone position increases the risk of SIDS is discussed below (see page 12 et seq).

4) Evidence for Infection and Inflammation in SIDS Pathogenesis

The above discussion reasonably excludes "respiration" as the primary point of failure in SIDS pathogenesis. However, there is room to consider the effect of proneness on brainstem-cardiac control. But it remains unnecessary to invoke a role for the brainstem in SIDS pathogenesis. Considering the risk factors that could trip the trigger to the fatal event in a susceptible baby (with inherited or acquired susceptibility), *infection* remains the most plausible as it has long been recognised as a risk factor for SIDS through symptomatology and signs of respiratory and/or gastrointestinal infection in the days preceding SIDS death (Hoffman et al 1988). Infection of normally sterile sites with major bacterial pathogens in SIDS has been independently described by two research groups.(Weber et al 2008, Goldwater 2008) This finding could represent the 'footprint' of a bacteraemic episode prior to death.(Goldwater 2011, Highet et al 2009) Bloodstream infection is a profound inducer of hypoxaemia; the

mechanism of which is not fully understood, however, the cytokine storm almost certainly plays a major role (Hotchkiss & Karl 2003) and the hypoxaemia the storm produces seems to precede the final demise in monitored SIDS cases. In addition, it is plausible that the findings of Vargas *et al.*(2013) in relation to *Pneumocystis* lung colonization/infection, with increased mucus production, could **contribute to hypoxaemia** but not necessarily be a direct cause of SIDS given that the fungus was found in a similar proportion of dead control babies (Vargas et al. 2007).

Of particular note is the fact that hypoxia is a driver of innate and inflammatory gene expression in host cells through activation of transactivation factors including NF-κB and Hypoxia Inducing Factor (HIF) (Schaible et al 2010) and thus proinflammatory cytokine perturbation could be contributory to arrhythmia, but with the knowledge that infection *per se* (respiratory or bacteraemic) is an inducer of proinflammatory cytokines, also acting through the NF-κB hub, the combination of hypoxia and infection could provide a fatal synergy.

Not only is infection (via sepsis or toxaemia) an inducer of hypoxaemia, it is also a key thermogenesis inducer and is usually overlooked by SIDS researchers married to linking prone sleep to respiratory physiology. On the other hand, supportive evidence for plausible links between prone sleep position and infection have been proposed based on bacterial colonization and toxin induction with raised nasopharyngeal temperatures prone, (Blackwell et al 2002, Molony et al 1999) and bacterial contamination of the sleeping surface promoting colonization of the infant's nasopharynx and gut (Blackwell et al 2002), Molony et al 1999, Goldwater 2003). From studies in a neonatal ward conducted many years ago, it has long been known that organisms, such as *E. coli* are shed into the air and onto surrounding furniture by infants and their care-givers and that these bacteria can then colonize other infants and sometimes cause serious infection (O'Farrell et al 1976). Furthermore, as skin scales decorated with *Staphylococcus aureus,* and coliform (e.g. *Escherichia coli*) bacteria are shed in "dangerous sleeping environments" (parental bed, sofa, etc.) it is not unreasonable to conjecture that prone babies will inhale or ingest these bacteria and thereby provide the first step in a pathway leading to SIDS via the so-called "Common Bacterial Hypothesis of SIDS" (Morris 1999) or via toxigenic effects of these bacteria, ,(Goldwater 2001, Highet et al 2009, Bettelheim et al 1989,1990,1991, 1995,2012, Goldwater & Bettelheim 2002, Highet & Goldwater 2009, Pearce et al 1999a, 1999b, 2004, 2010) or through abnormal/defective pathogen recognition (Highet 2009). (Goldwater 2001, Highet et al 2009, Bettelheim et al 1989,1990,1991, 1995,2012, Goldwater & Bettelheim 2002, Highet & Goldwater 2009, Pearce et al 1999a, 1999b, 2004, 2010) or through abnormal/defective pathogen recognition (Highet 2009). Baddock et al. (2004) highlight under the title What's known on this subject: "Sudden infant death syndrome remains the major cause of postneonatal death in developed countries. Although infant-parent bed-sharing following antenatal smoking or maternal consumption of alcohol on the bed-sharing night increases the risk of death, *the mechanism is not known*." The italics are ours, and it is to suggest that more is known than is suggested in this blank statement. We and our associates (Goldwater 2001, Highet et al 2009, Bettelheim et al 1989,1990,1991, 1995,2012, Goldwater & Bettelheim 2002, Highet & Goldwater 2009, Pearce et al 1999a, 1999b, 2004, 2010) as well as others (especially Drucker et al 1992, Bettiol et al 1994, Blackwell et al 2005, Jakeman et al 1991, Malam et al 1992, Sayers et al 1995) have shown that toxigenic organisms notably ones normally considered nonpathogenic commensals may well have an important role to play in the death of these infants. There is strong evidence to support the hypothesis that SIDS is triggered by a dysregulated response to infection or microbial toxins. In addition, if the various factors for SIDS are

analysed in relation to infection - age range, gender, prone sleeping position, lack of breast feeding, exposure to cigarette smoke, mild virus infection, ethnic group- there is evidence to support a role for infections and an infant's inflammatory response to these (Blackwell et al 2005). In regard to male gender and the increased risk of SIDS, a rise in testosterone levels is associated with the age prevalence peak of 2-4 months. Between one and 5 months testosterone levels in males exceed those in females (Soldin et al 2003). While androgens are well-known immunomodulators (Verthelyi 2001) their direct effect on bacterial growth has not been explored since it was shown that these hormones stimulate bacterial growth. An old study had shown that testosterone has a marked effect on the growth of *S. aureus.* Androgens (testosterone, testosterone propionate, and methyltestosterone) significantly promoted the growth of *Staphylococcus aureus* and *Corynebacterium pyogenes* (Hanifa Moursi 1966).

Can epidemiology of SIDS with respect to low and high incidence countries provide any clues in regard to the role of bacterial infection? Japan was renowned for a seemingly low incidence of SIDS but with an autopsy rate of less than 30% no reliance can be placed on that country's national figures (Sawaguchi et al. 2000). On the other hand, the high SIDS incidence in Australian and North American aboriginals and New Zealand Maoris provides indirect evidence of roles of both ethnicity and bacterial infection given that these communities have exceptionally high background rates of childhood bacterial infections (Blackwell et al. 2004).

Compared to an infant sleeping on its back in its own cot in a separate room, the infant sleeping prone in the same bed as its parent, who may have had one or more units of alcohol before going to bed and smoked a couple of cigarettes, this latter infant is likely to come into contact with far more potentially toxigenic bacteria than the aforementioned situation. Being in the same bed as the parent, the infant (prone or supine) will likely breathe in (or ingest) many of its parents' bacteria-laden skin scales and in the prone position acquisition of large numbers of these commensal bacteria-laden skin scales on the bedding/sleeping surface is quite likely. Cigarette smoke is known to enhance the toxigenicity of bacterial toxins (Sayers et al. 1995) as does respiratory viral infection (Jakeman et al 1991) and thus puts the infant at further risk. Furthermore, viral infection increases adherence of *S. aureus* to pharyngeal cells (Musher & Fainstein 1981). Excessive use of cigarettes and alcohol may also be an indicator of decreased standards of hygiene and less frequent changing of bed linen, which will again increase the amount of adult-derived skin scales carrying microorganisms for the infant to inhale or ingest. If spread of air-borne microorganisms did not occur then the problems of MRSA, *Cl. difficile* and norovirus in hospitals would not occur to the extent that they do, despite good levels of hand hygiene. Such microorganisms seem to have special features, in addition to their virulence factors, that promote epidemic spread. *E. coli* also can behave in this manner as was shown as long ago as 1983 (Bettelheim et al 1983). The basis of this property could lie in quorum sensing and could explain the SIDS "epidemic" of the 1980s. Thus we think that we have a plausible mechanism linking the well established risk factors of prone sleeping, bed-sharing, smoking and alcohol consumption (O'Leary et al 2013) with SIDS in genetically predisposed babies. It is now up to science to prove the null hypothesis! Considering that it is now theoretically possible to measure bacterial toxins in body fluids and tissues at autopsy, then, logically, if toxin is not detected then it is not the cause of death. On the other hand, if toxin is detected the pattern and dose of the bacterial secretome should distinguish genuine infection from postmortem contamination. SIDS research should uphold this approach by putting the paediatric autopsy back in its rightful place… at the centre of clinical academic medicine.

In relation to bed sharing (or particularly sofa-sharing), studies documenting the close physical positions (including face to face) of the co-sleeping mother and infant provide a reasonable explanation as to how the mother's respiratory and other flora (in terms of risk of pneumonia or diarrhoea in the infant) could be passed to the baby (Ngale et al 2013). Also in relation to bed sharing and smoking, smokers are more heavily colonized by potential pathogens identified in many infant deaths, e.g., *Staphylococcus aureus* (Musher & Fainstein 1981).

It has been previously pointed out how the risk factors can contribute to enhanced colonisation by bacteria, induction of temperature-dependent toxins, and control of inflammatory responses (Blackwell et al 2005). The effects of pro-inflammatory cytokines induced in response to infection (and to hypoxaemia) can affect all the physiological mechanisms proposed to explain SIDS. Our paper supports these previous studies and points out how social factors could contribute to susceptibility to infection.

We have demonstrated that a SIDS-like condition can be established in a murine model (Bettelheim et al 2012). This and the significant work on interactions between cigarette smoke, virus infection and responses to bacterial toxins that has been carried out by Blood Siegfried and colleagues (2004) in a rat pup model as well as the earlier studies by Jakeman et al (1991) should provide important answers to the underlying mechanisms and the various parameters can be studied in detail. Regrettably, many SIDS research funding bodies refuse to fund any laboratory animal investigation which has lead to a research road-block. We consider this impasse should be lifted if progress in SIDS pathogenesis is to be made. Mainstream researchers focussed on respiratory causes of hypoxaemia, could perhaps extend their vision to include infection as a legitimate underlying cause. By doing so, the next few years would likely be far more productive in terms of understanding the pathogenesis of SIDS than the last fifty.

Papers such as that of Krous et al. (2003) have incorrectly excluded infection as being important in SIDS pathogenesis on the basis of finding mixed bacterial isolates and inflammatory changes in both SIDS and controls. In addition, the microbiological results were not presented for independent interpretation. This and other studies that have compared the rate of infection in SIDS to control groups, however, show the rates tend to be equal amongst both populations; this apparent conundrum is easily explained by the presence of underlying risk factors in the SIDS group (e.g. especially genetic predisposition). **For any infectious disease, morbidity and mortality is a function of this underlying genetic make up, gender, age and nutritional status.** For SIDS, gender and age (and possibly nutritional status e.g. low vitamin D) play a role and more and more genetic factors are being discovered. The genome-wide multinational study currently underway should provide additional evidence in this respect.

Other evidence that supports the infection model in SIDS include waning transplacental maternal antibodies during the peak of SIDS at 2-3 months, sweat soaked clothing (and evidence of overheating… congruent with an infection-linked febrile event), low vitamin D levels adversely impacting on TLR-responses to infection (Walker et al. 2011; Cohen et al. 2013). In addition, subtle pathological evidence of myocarditis which could act in concert with brainstem derangement of the neurocardiac pathways as well as the stress of hypoxaemia arising from coincident lung infection and/or the effect of systemic bacterial infection or toxaemia is highly plausible.

Given the lack of any convincing information favoring an association between respiratory function, hypoxaemia and SIDS we consider it is high time for a re-evaluation of the direction of SIDS research and would recommend interested readers to go to http://www.biomedcentral.com/1741-7015/9/64. (Goldwater 2011).

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