Tragic and sudden death

Potential and proven mechanisms causing sudden infant death syndrome

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The death of a child is probably the most traumatic event any parent can experience. This tragedy is made worse if the child dies in its sleep, apparently for no reason. Sudden infant death syndrome (SIDS) inevitably strikes horror into parents' hearts; it usually happens at night and occurs in complete silence—there is no fight for life or breath to warn parents that something is horribly wrong. Indeed, infants who have died of SIDS look rather peaceful, which makes it even worse for parents who wake up in the morning to find their child dead.

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SIDS is not only a traumatic and devastating event for parents and medical examiners, it is also a cause of death that continues to thwart the efforts of scientists and physicians to prevent it, or at least to identify those children who are at risk. Indeed, the term SIDS was coined to provide a convenient diagnosis for a medical examiner to label an otherwise unexplainable death.

It is only during the past few years that scientists and epidemiologists have been able to identify environmental and metabolic factors that combine to cause SIDS. In particular, epidemiological research has identified some important environmental risk factors—notably when children sleep on their stomachs or under heavy blankets, or whether the parents smoke. One resulting recommendation is to encourage parents to turn infants on their backs; the 'Back to

Sleep' campaign that started in 1994 in the USA and similar educational campaigns in other countries have led to a considerable drop in SIDS deaths. Nevertheless, the prevalence of SIDS is still approximately 0.5% in the USA, or 50 deaths per 100,000 live births, and it still affects children who sleep on their backs. Therefore, the main objective of the ongoing research into the genetics, physiology and epidemiology of SIDS is to identify more risk factors.

In any case, SIDS is not a uniquely 'identifiable disease'; it is a diagnosis of exclusion that should only be applied to the death of an infant after an adequate post-mortem investigation—including an autopsy, a mandatory investigation of the death scene and an exploration of a possible family history—has provided no explanation. Indeed, the term 'sudden unexplained death in infants' is being increasingly used as it becomes evident that a number of deaths that were formerly termed SIDS were actually accidental suffocation, homicide, cardiac arrhythmias or inborn errors of metabolism.

SIDS is a combination of genetic, metabolic and environmental factors that culminate in the death of an infant. Not surprisingly, the literature abounds with many proposed mechanisms, theories and scientific concepts, which are rapidly changing. Nonetheless, researchers have been able to identify various prenatal and postnatal factors that increase the risk of SIDS (Sidebar A).

The greatest advances in elucidating the causes of risk for SIDS and formulating preventive measures have come through mandatory death scene investigations. In many cases, these often indicate that the airway of the child was compromised at the time of death. As further research establishes the

pathophysiology of various types of infant suffocation, the number of diagnoses of 'accidental suffocation', 'wedging' or 'positional asphyxia' have increased, whereas the formerly preferred diagnosis, SIDS, is now used less frequently. Unger and colleagues estimate that up to 30% of sudden unexplained deaths in infants can be attributed to accidental suffocation (Unger *et al*, 2003). Therefore, in recent years, there has been much attention paid to the various mechanisms that lead to accidental suffocation, including studies that have used mechanical models, animals and live infants to investigate how bedding obstructs air exchange.

When an infant's head is completely covered, or when it is lying face down into its bedding, exhaled air can be trapped to a varying extent (Unger *et al*, 2003; Patel *et al*, 2001). The child re-breathes the exhaled air, which, over time, leads to high levels of carbon dioxide and increasingly low levels of oxygen in the air pocket formed between the infant's head and the bedding. For infants who sleep face down, the softness of the bedding determines the depth of this air pocket—the deeper the pocket, the greater the seal around the face and the less likely the chance that there will be air channels to allow access to fresh air. For infants whose head is covered, the thickness of the bedding determines the size of the trapped pool of air. If the bedding beneath the face or over the head is thin, an increase in tidal volume might be sufficient to prevent asphyxia—a dangerous depletion of oxygen in the blood—whereas a single heavy blanket might be sufficient to cause asphyxia.

Another crucial factor is an infant's own protective response, which is learned by

experience (Paluszynska *et al*, 2004). Most infants who normally sleep face down frequently experience re-breathing during a single night and learn to lift or turn their head to the side. Infants who have never slept prone often fail to turn their heads to the side. Although they might lift their heads, this lasts for only a few seconds and they then continue to re-breathe exhaled air once their heads drop down (Paluszynska *et al*, 2004).

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Once in a re-breathing environment, the rate of progression is highly variable. Slight changes in head position might create new air channels in the bedding to allow access to fresh air. If the infant does not move the head, the progression of asphyxia is usually slow and occurs over several minutes or longer. Arousal is usually accompanied by a sharp decrease in respiratory frequency. When this happens, the oxygen saturation might drop rapidly to 85% or less. Once oxygen saturation reaches 30–40%, the brain is depleted of oxygen, hypoxic coma occurs and arousal is no longer possible. Even autoresuscitation by gasping is ineffective when the infant's head is in a hypoxic environment.

Another documented cause of death is the compromising of an infant's airway by a sleeping parent or sibling when bed sharing; in recent years such deaths have increased as bed sharing has become more popular and could explain as many as 50% of sudden unexpected infant deaths (Unger *et al*, 2003; Blair *et al*, 2006). The presumed mechanism of death is accidental suffocation by close contact with a co-sleeper. However, the actual cause of death in this situation is usually very difficult to prove.

As mentioned above, educational campaigns with the aim of preventing both prone sleeping and bed sharing have led to a significant decrease in the number of infants dying from suffocation. Nevertheless, SIDS still occurs in seemingly healthy children, even if they sleep on their backs. The main focus of research

is therefore to identify other risk factors and to investigate possible pathophysiological mechanisms, as well as theories of how various factors contribute to and cause SIDS. A plausible mechanistic theory is essential to develop diagnostic tests to accurately identify children at risk and, eventually, to develop preventive or therapeutic measures (Leiter & Böhm, 2007).

Another suspected precursor to sudden death in infants is heat stress—extreme elevations in body temperature that can cause fatal heat stroke. The idea that heat stress itself can result in SIDS is based on data from countries where it is common to dress infants in many layers of clothing or to cover them with quilts during the winter (Mitchell *et al*, 1991; Fleming *et al*, 1996). Because the face is a main source of heat elimination, it has been suggested that infants who are face down can die from heat stress. Proponents of this theory believe that heat stress might not necessarily be associated with an actual elevation in body temperature.

However, several observations argue against heat stress as being a major cause of SIDS. As dangerous asphyxia can occur very soon after an infant turns its face into the bedding, it would seem that this might cause death before the heat stress could take effect. This, of course, does not eliminate the possibility that a combination of elevated body temperature and re-breathing might be more lethal than either factor alone. In the USA, SIDS rates do not increase during summer heat waves when the country witnesses a marked increase in heat-related deaths (Scheers-Masters *et al*, 2003), which indicates that heat stress is not a main cause of SIDS, at least in the USA. Finally, perhaps the greatest problem with the heat stress theory is that there has been no pathophysiological mechanism identified so far that could cause sudden death.

The eventual cause of death in SIDS infants is a failure to breathe. However, this should not happen: humans, as well as many animals, have evolved highly effective emergency reflexes to spontaneously recover from severe hypoxia (Thach *et al*, 1991). If hypoxia turns into coma, cortical activity in the central nervous system and most brain-stem-mediated reflexes cease to function. This triggers a set of emergency reflexes that eventually reinstate normal respiration by intermittent hypoxic gasps that, in the

Sidebar A | Factors that increase the risk of sudden infant death syndrome (SIDS)

Prenatal risks

Inadequate care
Inadequate nutrition
Smoking
Use of heroin
Subsequent births less than 1 year apart
Alcohol abuse
Obesity

Postnatal risks

Low birth weight
Exposure to tobacco smoke
Sleep positioning
Excess clothing and overheating
Excess bedding, soft sleep surface and stuffed animals
Gender (61% of SIDS cases occur in males)
Age (highest from 2 to 4 months)
Premature birth

absence of compromised lung or cardiovascular function, provide enough oxygen for the body to reinstate normal function.

SIDS is a combination of genetic, metabolic and environmental factors that culminate in the death of an infant

Several studies have analysed recordings of cardiac and respiratory activity just prior to the death of infants who have died of SIDS and other causes (Poets *et al*, 1999; Sridhar *et al*, 2003; Meny *et al*, 1994). Of the 18 or so SIDS deaths analysed so far, there have been only two cases in which the child failed to breathe before the onset of hypoxic gasping—in these cases, the lack of breathing might have caused the hypoxia. These home-monitored recordings showed an abruptly slower heart-beat—bradycardia—just before the onset of apnea—the suspension of breathing. This suggests that the preceding hypoxia was severe and already present during the 15-second period captured on tape just before the bradycardia; it is not clear what caused the infant to become hypoxic. It is relevant that, compared with infants dying of other causes, these SIDS infants showed a decreased ability to transiently increase their heart rate or recover normal breathing as a result of hypoxic gasping (Sridhar *et al*, 2003), although it is still not clear why autoresuscitation failed.

Infants born prematurely are notoriously susceptible to episodes of apnea, which can be generally distinguished into two types. Awake apnea is attributed to acute hypoventilation associated with breath holding as a result of pain or emotional upset (Abu-Osba *et al*, 1982). Such spells can result in sudden severe hypoxia with secondary hypoxic apnea. However, once the body's emergency mechanisms kick in, the children autoresuscitate by gasping. Indeed, the hypoventilation associated with ordinary crying has many similarities to clinical breath holding, which is often preceded by crying. Breath holding during arousal from sleep is a common cause of oxygen desaturation in pre-term infants (Abu-Osba *et al*, 1982). Although SIDS is believed to occur when infants are sleeping, the potential role of brief arousal accompanied by breath holding with severe hypoxia and failed autoresuscitation cannot be excluded as a cause for some SIDS deaths.

The second main type of apnea occurs primarily during sleep. The most important of these are obstructive sleep apnea (OSA) and reflex apnea caused by laryngeal chemoreflexes (LCRs; Pickens *et al*, 1988; Davies *et al*, 1988). As the muscle tone of the body ordinarily relaxes during sleep, the soft tissues that make up the walls of the human throat can collapse, thereby causing OSA, which, in a mild form, is quite common. LCRs are stimulated by hypochloride or acid solutions from the stomach content that contact mucosal nerve endings at the entrance to the larynx. They consist of apnea, swallowing, laryngeal closure and coughing. Unlike OSA, apnea in premature infants predominantly consists of respiratory pauses associated with sporadic obstructed breaths. It is usually associated with swallowing during the spell, a characteristic of LCR apnea, but it is not known to happen during OSA (Pickens *et al*, 1988).

Studies of sleeping human infants, stimulated with water infused into the pharynx, have shown that repeated swallowing, apnea and airway obstruction occurs more often in pre-term infants (Pickens *et al*, 1988; Davies *et al*, 1988). Furthermore, several studies have found that apnea and bradycardia associated with swallowing and intermittent airway obstruction occur spontaneously during sleep in pre-term infants, even in the absence of any detectable stimulus (Pickens *et al*, 1988; Miller & DiFiore, 1995). Apnea can also occur through regurgitation of the stomach content. This suggests that endogenous

stimuli from accumulated pharyngeal secretions or regurgitated gastric fluid can elicit LCR responses in pre-term infants (Pickens *et al*, 1989). Apnea therefore remains a viable hypothesis for sudden death in infants. In fact, a few of the home recordings of SIDS cases indicate that apnea preceded death (Poets *et al*, 1999; Sridhar *et al*, 2003; Meny *et al*, 1994). The apnea hypothesis is also strengthened by the observation that its persistence is much stronger in pre-term infants who are at an especially high risk for SIDS (Hunt *et al*, 2004).

Infection—particularly with the respiratory syncytial virus (RSV)—is another factor that is strongly suspected to trigger the fatal course of events that lead to SIDS. RSV is known to cause severe LCR-induced apnea, and infected infants occasionally require mechanical ventilation to prevent death. Furthermore, infants between two and four months of age actually have a significantly decreased number of red blood cells, which can greatly prolong LCR apnea (Fagenholz *et al*, 1979). Together, these facts suggest that viral infection with RSV and other viruses at the peak of prematurity anaemia could cause SIDS.

It seems that most SIDS infants had multiple abnormalities in brain serotonergic systems, which could provide an explanation for why they were more vulnerable to death

In support of the argument that viral infection could be a precursor for at least some cases of SIDS, Vege & Rognum (2004) reported increased levels of interleukins in the cerebrospinal fluid of many SIDS victims. Other studies associated RSV infection with increased LCR reflexes and an increase in inflammatory interleukin in the laryngeal mucosa. It remains to be seen how increased interleukin in the brainstem might cause sudden death, but these observations support the theory of subtle infections as an initial cause of apnea and eventually SIDS. There is also epidemiological support for this theory: seasonal outbreaks of RSV during the winter months coincide with a peak of SIDS cases. Together, this would make a strong but circumstantial case for upper-airway infections that cause LCR apnea as the mechanism for the increased SIDS incidence in the winter.

Some have speculated that OSA could also cause sudden death in infants because the vast majority of SIDS infants are presumed to die during their sleep and OSA is entirely a sleep-dependent disorder (White, 1995). Indeed, the severity of OSA increases with viral infections of the upper airway, which increase nasal resistance. Moreover, epidemiological studies found that a family history of OSA is a risk factor for SIDS (Tishler *et al*, 1996) and that brief episodes of OSA were more common in infants who ultimately died of SIDS (Kahn *et al*, 1992).

Two main physiological risk factors for SIDS are heart defects or heart irregularities that, in combination with breathing difficulties, eventually lead to death. One prominent theory proposes that some SIDS infants might have inherent cardiac conduction defects (Schwartz *et al*, 1998), notably a prolonged so-called QT interval in the heart's electric cycle, which would render the heart susceptible to ventricular fibrillation. Although most patients spontaneously recover from ventricular bradycardia or fibrillation, some can die a sudden death even in the absence of any preceding symptoms (Towbin & Ackerman, 2001). Several genetic mutations in sodium ion or potassium channels in the myocardial cell membrane cause prolongation of the QT interval (Wang *et al*, 2007). Of relevance to SIDS, some of these genotypes are associated primarily with death during sleep. The triggering event might be emotional excitement when awake or a sudden stimulus causing arousal from sleep.

There is a large body of evidence to support the idea that a prolonged QT interval has a causal role in SIDS. First, a prolonged QT in the first week of life is strongly associated with SIDS (Schwartz *et al*, 1998). Second, infants who have died suddenly and unexpectedly have often had a prolonged QT interval before death. Third, 4.3% of infants who died of SIDS in a large case study had pathological QT mutations (Towbin & Ackerman, 2001; Wang *et al*, 2007). All in all, these findings provide strong evidence that a minority of deaths in infants is caused by genetic mutations that prolong the QT interval and cause fatal ventricular bradycardia or fibrillation.

Infants who die from inherited metabolic disorders are technically not SIDS cases. Nevertheless, when an autopsy cannot reveal a clear cause of death, it is often concluded as SIDS. So far, several

metabolic defects are known to be risk factors for sudden death, such as medium- and long-chain acyl-CoA dehydrogenase deficiency, glutaric acidemia type 1 and 2, and carnitine palmitoyl transferase type II/translocation deficiencies. Most infants with these disorders suffer from acute metabolic problems but, when admitted to a hospital, they respond rapidly to medical therapy. Furthermore, most medical examiners now screen for metabolic defects at the post-mortem examination. In the past, approximately 3–6% of sudden infant deaths were the result of such metabolic disorders (Boles, 2001). However, as post-mortem diagnoses are becoming more frequent and accurate, the number of these deaths diagnosed as SIDS is becoming less frequent.

The past decade has seen much research into brainstem defects in SIDS infants to explain the failure of the body's own emergency mechanisms to autoresuscitate an infant that has stopped breathing (Kinney *et al*, 2001; Ozawa & Okade, 2002). Various studies have identified subtle anatomical changes and receptor deficiencies in brainstem nuclei in infants who have died of SIDS. In many cases, certain nuclei, which are believed to be critical for carbon dioxide sensitivity, arousal from sleep and cardiorespiratory control, were shown to have decreased numbers of serotonergic receptors compared with those in infants dying from other causes. Other studies of SIDS infants have documented inherited defects in serotonin transporter genes (Narita *et al*, 2001; Maher *et al*, 2006).

Current theories therefore explain SIDS through a combination of environmental, genetic and metabolic factors that do not cause SIDS themselves, but render an infant more vulnerable

It seems that most SIDS infants had multiple abnormalities in brain serotonergic systems, which could provide an explanation for why they were more vulnerable to death (Paterson *et al*, 2006). However, the numbers of neurons that are deficient in serotonin receptors are actually increased in SIDS infants, which might be

a compensation for the reduced serotonin receptors on individual neurons (Paterson *et al*, 2006). As such, these infants might not have abnormal brainstem function. At the current stage of research, it is not clear whether these altered serotonin transporter genes have any pathological significance or represent a possible genetic predisposition to SIDS (Leiter & Böhm, 2007).

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Nonetheless, these brainstem abnormalities might explain why autoresuscitation fails when infants reach a critically low level of oxygen saturation in their blood. Further research in this area has concentrated on the possible deficiencies that would prevent arousal from sleep and related carbon dioxide sensory mechanisms.

These efforts are justified by reports that the arcuate nucleus of the brainstem in a few SIDS infants showed hypoplasia—that is, incomplete development (Filiano & Kinney, 1992). This area of the brain is believed to be a major site of carbon dioxide-sensitivity regulation related to respiratory function. However, experiments using antagonists of the specific serotonin receptor sites in the brain have produced only modest decreases in carbon dioxide sensitivity (Curran *et al*, 2001). Moreover, the reduced carbon dioxide response is seen only in male infants (Pematti *et al*, 2006). Therefore, as far as the response to increasing levels of carbon dioxide is concerned, it is unclear how a reduction in serotonergic receptors could significantly increase the risk for SIDS. More generally, it is not clear how brainstem serotonergic mechanisms might increase vulnerability to SIDS. In summary, it seems that abnormal serotonergic systems in the brainstem of many SIDS victims could prevent arousal from sleep, or cause alterations in sleep state cycles, cardiovascular control or carbon dioxide responsiveness (Darnall *et al*, 2005). At present, it remains to be seen how such abnormalities could make infants substantially more vulnerable to SIDS.

Current theories therefore explain SIDS through a combination of environmental, genetic and metabolic factors that do not cause SIDS themselves, but render an infant more vulnerable (Guntheroth & Spiers, 2007). A viral infection, LCR apnea or OSA could trigger an eventually fatal chain of events that start as the child's emergency responses to critical oxygen concentration in the blood fail to kick in.

So far, the greatest progress in preventing the sudden and unexpected death of infants comes from epidemiological research to identify environmental risk factors, and campaigns to educate and advise parents. In particular, the use of lighter bedding and the turning of sleeping infants onto their back have both greatly reduced the number of SIDS cases and accidental suffocation in many countries. However, SIDS is still the second leading cause of early childhood death, after congenital disorders, and the leading cause of death in babies aged between one month and one year. Further progress thus depends on the identification of genetic, metabolic and physiological risk factors, and their exact role in increasing an infant's vulnerability to sudden death. Yet, without solid biological and mechanistic theories of how these various factors combine and act, it remains difficult to develop reliable diagnostic tests to identify vulnerable children, let alone develop preventive therapies. Given the number of infants each year who still die of SIDS, and the traumatic experience that results for their parents, it is a research topic with both a noble goal and potentially huge benefit for society.

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