Some controversial theories for SIDS

Mechtild MT Vennemann[1], T. Fracasso[1], EA Mitchell[2]

Authors' affiliations

[1]Institute of Legal Medicine, University of Münster, Röntgenstr. 23, 48149 Münster

[2]Department of Paediatrics, University of Auckland, Private Bag 92019, Auckland, New Zealand.

Corresponding author: Dr Mechtild Vennemann

Contact details

Email: Mechtild.Vennemann@ukmuenster.de

Phone: 0049-251-835 2928

Fax: 0049-251-835 5158

Abstract

Almost 20 years ago prone sleeping position was established as a risk factor for sudden infant death syndrome (SIDS) and with risk reduction campaigns which largely focused on this one factor, the incidence of SIDS has declined by 50-80% in most of the countries where campaigns were conducted. However, the pathophysiological cause or causes of SIDS are not yet known, although many theories have been proposed. This paper examines several of the more controversial theories for SIDS causation.

In 1997 a link between Helicobacter pylori and SIDS was proposed. Initial positive results were not confirmed. More recently there is new evidence that H. pylori may play a role in some cases but these results need to be confirmed by others. Anaphylaxis caused by milk is an older theory, which has its merits, but needs to be verified with new methods. The toxic gas theory was interesting but had flaws. “Toxic gases” have not been produced in an environment remotely resembling that found in a cot. Proponents of the theory have recommended wrapping the cot mattress in polythene to prevent the postulated gases reaching the baby, but there is no evidence that this has had any effect. The proponents have been very vocal in the lay media despite evidence that disproves this theory. No further evidence is needed for the final rejection of this theory. The harm and benefits of immunisations are a controversial topic in the lay press, although seldom in the scientific literature. As the age of infants dying from SIDS is similar to that when immunisation is given, it has been postulated that there is a causal link. Several large case-control studies have shown that immunisations are not a risk factor for SIDS and recent a meta analysis in fact reported that immunisation halve the risk for SIDS compared with infants who had not been immunized.

In conclusion, while the cause or causes of SIDS remains unknown new theories will be proposed and this is to be welcomed. These theories should be first discussed within the scientific community. Debating theories and preliminary findings in the lay media risks confusing parents of young infants and takes attention away from established risk factors and recommendations.

Introduction

Epidemiological studies have been very successful in identifying risk factors for sudden infant death syndrome (SIDS) (1-6). Risk factors are not necessarily causal; however there is good reason to believe that prone sleeping position is causally related to SIDS, as the reduction in the prevalence of infants sleeping in the prone position has been associated with a remarkable reduction in SIDS and postneonatal mortality. Epidemiological studies do not tell us the pathopysiological mechanism of SIDS, although they may provide clues of the mechanism (7-9). SIDS is by definition unexplained (10), and many theories for causation have been proposed, some of which have sound basis and others with less evidence.

This paper examines some of the more controversial theories for SIDS, in particular focussing on the role of Helicobacter pylori, the toxic gas theory, anaphylaxis and immunisations.

The role of Helicobacter pylori

The hypothesis of a link between Helicobacter pylori (H. pylori) and SIDS was firstly advanced by Pattison and Marshall in 1997 (11). Infection could occur from mother or other family members through saliva exchanges (drooling by siblings or handling and using bottles and pacifiers). The authors postulated that repeated gastro-oesophageal reflux, typical of the first months of life, could result in aspiration of gastric content and H. pylori colonies producing high amounts of urease. The interaction between bacterial urease and plasmatic urea in the lungs would lead to ammonia production that could be rapidly fatal. They found H. pylori in the gastric and tracheal mucosa by immunohistochemistry in 6 of 7 SIDS cases. The study was repeated in a further 33 cases and H. pylori was found in 20 (66%) of cases but only 2 (33%) of 6 controls (12).

The relationship between H. pylori and SIDS has been further investigated by other groups. In 2001 Elitsur et al (13) failed to identify H. pylori infection in a series of 25 SIDS cases after histology, immunohistochemistry and polymerase chain reaction (PCR) amplification on formalin-fixed paraffin-embedded (FFPE) specimens of gastric and tracheal mucosa. In 2000 Kerr et al (14) compared 32 cases of SIDS to 8 controls. The authors were able to amplify by PCR H. pylori genome in FFPE specimens from SIDS cases thus supporting the theory of H. pylori infection. In 2001 Ho et al (15), from the original research group that firstly proposed the theory of H. pylori infection and SIDS, published a prospective study on 9 SIDS cases in which they could not demonstrate any association between H. pylori and SIDS after histology, rapid urease (CLO test), bacterial culture and PCR amplification. In light of these new investigations the authors believe their preliminary results were due to possible contamination or false positive findings. Similar results were later obtained by a German group (16) in a large retrospective cohort of 94 SIDS cases. The highly specific real time PCR method applied for DNA amplification from FFPE tissue could not demonstrate any association between H. pylori and SIDS.

More recently Stray-Pedersen et al (17) detected H. pylori stool antigen (HpSA) in 52% of 69 investigated newborns (0-2 days). Seropositivity was 15% in children aged 7 days-1 month and 5% in those aged 1 month-3 years. The detection rate varied

significantly with age (P<0.001), suggesting transient colonisation in the neonate. To verify their results the authors analysed 26 HpSA positive cases and 26 negative controls with PCR targeting the 16 s rDNA Helicobacter gene. Positive PCR results were found in 35% and 12% respectively. A high rate of HpSA in SIDS cases compared to living controls was subsequently reported by the same group [9]. Moreover HpSA positive SIDS victims also showed higher Interleukin 6 (IL-6) cerebrospinal fluid (CSF) levels compared to HpSA negative SIDS cases. An exaggerated immune response with abnormal cytokine cascade has been repeatedly discussed as a potential cause of SIDS (18;19). The authors conclude that H. pylori may play an important role as a trigger for sudden death during the first five months of life.

The hypothesis of an involvement of H. pylori in the pathogenesis of SIDS is intriguing because it could explain many of the established risk factors for SIDS; the prone sleeping position could increase aspiration of refluxed gastric content and low socioeconomic level is associated with increased infection. Moreover some pathological changes described in SIDS, such as increased levels of IL-1 and 6 which indicates activation of the immune system, could be produced H. pylori infection.

The published results are on the whole contradictory. On one hand evidence of infection with H. pylori has been reported in several studies with various methods including immunohistochemistry and the detection of stool antigen. On the other hand, PCR amplification has up to now substantially failed to show evidence of H. pylori infections in SIDS cases. This technique has been however only been applied at FFPE specimens (20). Further studies including PCR amplification from fresh material may in the future help to identify the role of H. pylori in the pathogenesis of SIDS.

Toxic gas theory

The toxic gas theory was initially proposed in 1989 by Mr Barry Richardson in the lay media and published as a letter in 1990 (21) . The theory was more extensively presented in 1994 (22) . It was an interesting theory, which warranted investigation.

Richardson proposed that the chemical compounds of phosphorus, arsenic and antimony, either present naturally or added as flame retardants or fungicides to cot mattresses or covers, might undergo microbial biomethylation forming toxic volatile compounds (phosphines, arsines and stibines). Specifically a fungus (*Scopulariopsis brevicaulis*) was implicated as being present on older, previously used mattresses. In fact the biomethylation of arsenic products leads to the production of trimethylarsine rather than the very toxic arsine. There is limited evidence that stibines can be produced and none that phosphine can be produced. No-one has shown that the toxic gases can be produced in any environment resembling that found in the infant cot (23;24). Recently, it has been pointed out that trimethylarsine has very low toxicity (25).

Proponents of the toxic gas theory used the media to promote the theory. Two comprehensive commissioned reports from the United Kingdom into the theory, including original research, concluded that the hypothesis was unsubstantiated (26;27).

There are many pieces of evidence that lead to the conclusion that the theory is wrong. Firstly, central to the theory is the presence of the fungus. Mattress contamination with *S. brevicaulis* is rare and no more common on SIDS mattresses than on mattresses used by infants who died from SIDS. (28). Secondly, the theory cannot explain the characteristic commonly associated with SIDS, for example the winter peak, or the higher risk in infants whose mothers smoked, were bottle-fed, were bed sharing, or who had intrauterine growth retardation.. Thirdly, SIDS events occur in environments where infants sleep, including places where fungal contamination is unlikely e.g. parent’s arms, parental bed. Fourthly, the pathological findings at autopsy are not those found in poisoning by these gases (29).

Proponents of the toxic gas theory have recommended wrapping cot mattresses in polythene since 1994 and have claimed that this action has lead to the continued reduction in SIDS since 1994. In New Zealand SIDS mortality declined 63% from 1994 to 2004. A recent survey has shown that the use of plastic wrapped cot mattress covers has remained constant at about 22% between 1997 and 2005 in Auckland, New Zealand. Even if mattress wrapping was completely effective in

preventing SIDS it could only produce a 22% reduction in SIDS compared with the 63% decrease in SIDS seen, unless those that used plastic wrapping were at high risk of SIDS. In fact the opposite was seen. They were more likely to be European, sleep their baby supine, not bed share and be a non-smoker. All these factors are associated with a reduced risk of SIDS (23). In contrast the proportion of infants sleeping on their back has increased substantially, and this could account for between 39% and 48% decrease in SIDS mortality (30).

There are potential dangers of wrapping the cot mattress in polythene. The major concern is that babies might suffocate on the plastic wrapping. Although the risk is low, this has to be balanced against the lack of evidence of benefit. There has been at least one death from asphyxia in New Zealand from the thin polythene sheeting, which the parents had used in the belief that this would protect against SIDS.

Anaphylaxis

In 1960 Parish and Coombs put forward the hypothesis that allergy to milk might be involved in the death of the infants who died from SIDS (31). It was suggested that sensitized infants suffer an anaphylactic reaction when milk is regurgitated and inhaled during sleep.

In 2001 Buckley et al reported a study of 40 SIDS infants and 32 infants with known causes of death and found that ß-tryptase (a protein that is released from mast cell granules during anaphylactic reactions) was elevated but not α-tryptase. He concluded that anaphylaxis may play a role in some SIDS cases (32). Tryptase is normally expressed by human mast cells and basophils. α-tryptase and ß-tryptase levels in serum are clinical tools for the evaluation of anaphylaxis (33).

The choice of the control group is problematic as severe trauma increases histamine and tryptase levels (34). The control group of Buckley included non-accidental injuries and asphyxial death.

Edston et al (35) examined 44 infants younger than 1.5 years for mast cell tryptase and total immunoglobin (Ig) E. In 40% of the SIDS cases tryptase was elevated, but the only variable associated with a high tryptase was prone sleeping position. They concluded that this was likely to be due to a hypoxic stimulus in these infants. Nishio

and Suzuki (36) measured tryptase in 21 SIDS victims and 14 control infants and found no elevated levels in the SIDS infants compared to controls. Additionally increased concentrations of tryptase were not observed in any SIDS case. They concluded that anaphylaxis is not involved in the aetiology of SIDS.

The evidence that anaphylaxis is a major factor in the SIDS aetiology is inconclusive But with newer technologies, like immunohistochemistry and milk specific IgE, it should be possible to determine levels of tryptase and and/or chymase in a larger sample.

Immunisation

The association between SIDS and immunisations are frequently discussed, especially in the lay press (37). The majority of SIDS cases occur between the second and the 5th months of life. This is also the time when the first immunisations are administered. This temporal association has lead to the assumption that the cause of death for these infants is the immunisations. In a letter to the Editor of "Vaccine" Zinka et.al. reported 6 cases who had died soon after vaccination and had an abnormal brain oedema (38). In their letter they warned the vaccinating physicians and paediatricians about these possible side effects of vaccination, but stated in the same letter that there is no proof that the vaccinations had caused the death of these children. The letter was heavily criticised by the scientific community as they did not described the cases in detail, nor describe the interval between immunisation and death. They did not describe the autopsy protocol and the "extraordinary" brain oedema was not compared with to any valid reference. Furthermore the literature they cited for a possible connection between brain oedema and pertussis vaccines was more than 20 and 35 years old (39;40).

In several well conducted case-control studies the association between immunisations and SIDS has been examined (41-49). None of them found an increased risk with vaccination. Four from these 9 case-control studies found a statistically reduced risk in the univariate analysis. A meta-analysis found that the combined univariate OR for vaccination was 0.58 (95% CI: 046-0.73). In the

multivariate analysis this meta-analysis was able to use data from 4 large studies and found that the risk of SIDS is halved in vaccinated infants (50). This is currently the best evidence that immunisations are not a risk but indeed can reduce the risk for SIDS and therefore should be included in the prevention programs.

Conclusions

Despite the reduction in SIDS the cause or causes of these sudden deaths remains a mystery. Many SIDS theories are published without any qualification in the lay media. Some of these theories are given even more prominence than the theories which have considerable support (6). Not surprisingly parents of young infants are confused by these theories which are sometimes conflicting. The media has a responsibility not to publicise a theory which is not scientifically supported and that is contrary to the established SIDS prevention messages.

SIDS researchers should be aware of their responsibility to only give evidence based advice. It is important that new theories are developed but every new theory needs to be verified by independent groups preferable in different countries. The appropriate place for debate is in the scientific literature, not the lay media.

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