

SUDDEN INFANT DEATH SYNDROME

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INTRODUCTION

The sudden infant death syndrome (SIDS) is the leading cause of postperinatal infant mortality in the UK. There are approximately 1500 deaths per annum. There have been many theories advanced over the years to explain the condition but the cause is still not known. Indeed, as in other areas of medicine, the rate of progress and depth of understanding seem to be inversely related to the number of theories proposed.

The condition is diagnosed when a baby dies suddenly and unexpectedly and a detailed autopsy fails to reveal an adequate explanation for death. It is important to stress that the diagnosis is made by exclusion and therefore it is possible that the syndrome includes a number of different conditions and modes of death. In fact it has become fashionable to stress that SIDS could have many different causes and that it is not a single disease. There are, however, some strikingly consistent and characteristic epidemiological features of SIDS such as the seasonal incidence and the age incidence. Thus there must be factors in common in enough cases to impose the epidemiological pattern. In this article I shall review evidence implicating infection as a "factor in common" and I shall describe some research which is being undertaken locally to investigate a specific hypothesis concerning bacterial infection.

VIRAL INFECTION

There is persuasive evidence that viral infections of the respiratory tract are causally related to SIDS. There is a striking seasonal pattern with an increased number of cases in the winter months when viral respiratory infections are more prevalent (Fig 1). In addition a number of workers have noted an increased incidence of SIDS at times of viral epidemics in the local community and if detailed histories are taken from the families of cases of SIDS there is often evidence of viral infection in the infant or in other family members around the

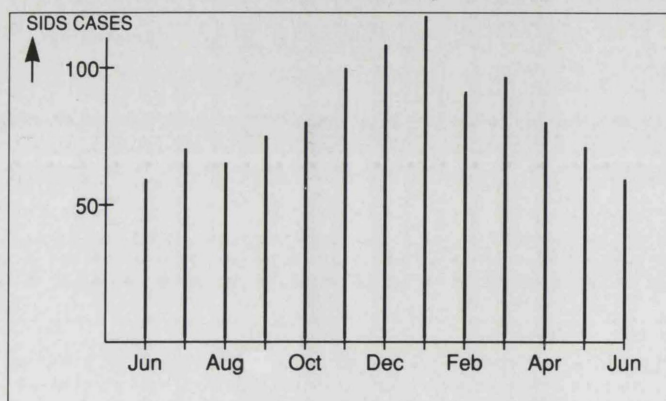


Fig 1 - Cases of SIDS by month

time of death. Furthermore, mild inflammation of the upper and lower respiratory tract is commonly found at autopsy.

There have been a number of virological investigations of SIDS. In up to 40% of cases viruses have been isolated from respiratory secretions. The viruses identified include respiratory syncytial virus, adenovirus, influenza, parainfluenza and rhinoviruses.

AGE INCIDENCE

The single most consistent and characteristic feature of SIDS is its age incidence (Fig 2). In every major study the number of deaths rises to a peak at two to three months and then falls rapidly so that the disease is uncommon after six months and rare after twelve months. It is possible to explain this curve in terms of infection. Maternal IgG protects against infection in the early weeks of life so that the risk of infection will rise as maternal IgG levels fall. The risk of infection will then fall as infants meet and acquire immunity to common organisms. But if immunity is virtually complete by the end of the first year then, of course, the causative organisms must be extremely common.

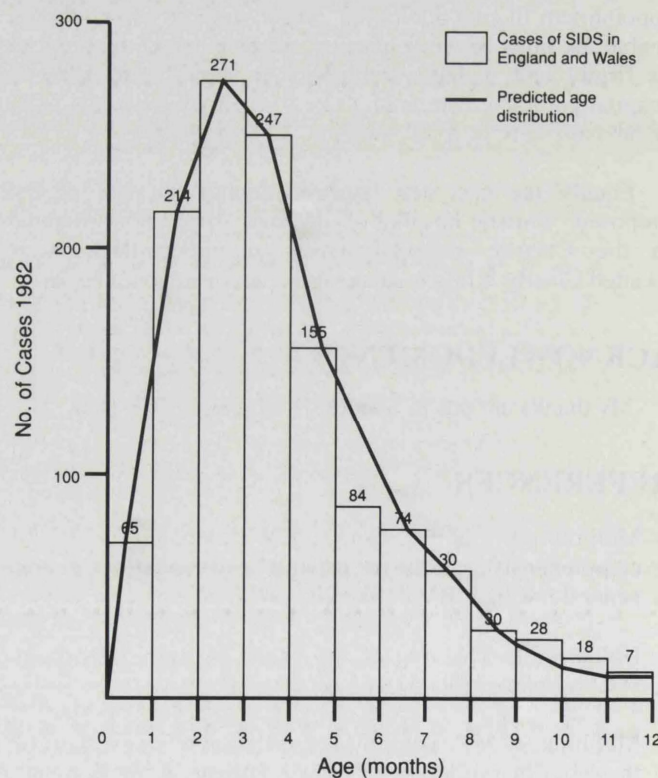


Fig 2 - The number of cases of SIDS in England and Wales in 1982 together with a theoretical curve based on a mathematical model

It is possible to make this explanation more precise by using a simple mathematical model¹. In this model the rate of fall of maternal IgG determines the rising rate of infection, whilst the rate at which infants encounter the putative causative agent determines the falling rate of infection. A theoretical curve produced by this model gives a close fit to the observed age distribution (Fig 2). To produce this fit, however, it is necessary to assume that 50% of the population meet the causative agent in fifty days, ie the causative agent is very common.

This is an important point because the viruses that cause respiratory infection are far less common. There is no single virus that 50% of the population meet in any fifty day period. This is true of even the most common viruses such as respiratory syncytial virus. It is even true of enteroviruses in tropical countries. The only organisms which are sufficiently common are bacteria which colonise the body surface in the early days and weeks of life. Thus if the age incidence curve of SIDS is to be explained in terms of infection it is bacterial, not viral, infection which is the determining factor.

The mathematical model becomes more complicated if synergistic combinations of organisms rather than single organisms are involved. The general principle, however, remains that some of the organisms must be very common and therefore must be bacteria rather than viruses.

BACTERIAL INFECTION

A great deal of work has been done to investigate the role of bacteria in SIDS. The initial studies were concerned with trying to find evidence of overwhelming invasive bacterial infection such as pneumonia, septicæmia, meningitis and pyelonephritis. The conclusion of these studies was that if an intensive bacteriological investigation is undertaken there is evidence of invasive infection in 10% of cases, but in 90% of cases invasive bacterial infection is not found.

More recently the focus of research has been on the role of bacterial toxins produced by bacteria growing on the body surface. Recognition of the toxic shock syndrome in adults has dramatically illustrated the fact that toxins can cause severe disease and even death in the absence of bacterial invasion. It seems reasonable to suggest that infants, in the short period following loss of maternal IgG, might be particularly susceptible to the lethal effect of absorbed toxins.

The first evidence that this could be important came with the realisation that *Clostridium botulinum* colonisation of the gastrointestinal tract in infancy could lead to sudden death². The mechanism is botulinum toxin absorption leading to respiratory paralysis. A number of studies have shown that between 0% and 9% of SIDS cases are due to botulinum toxin depending on locality. This condition is extremely rare, however, in the UK.

Arnon has pointed out that there are a great many other toxigenic bacteria which are commonly found in the gastrointestinal tract and that these could also lead to SIDS. In fact he has suggested that most cases of SIDS arise in this way. This idea has a great deal to commend it but how does this concept fit with the evidence noted above that viral respiratory tract infections also have a key role in SIDS?

A UNIFYING HYPOTHESIS

It is possible to combine the concept that viral respiratory infections are important in SIDS with the idea that bacterial

toxins might also have a role to produce a unifying hypothesis. This is illustrated in Figure 3.

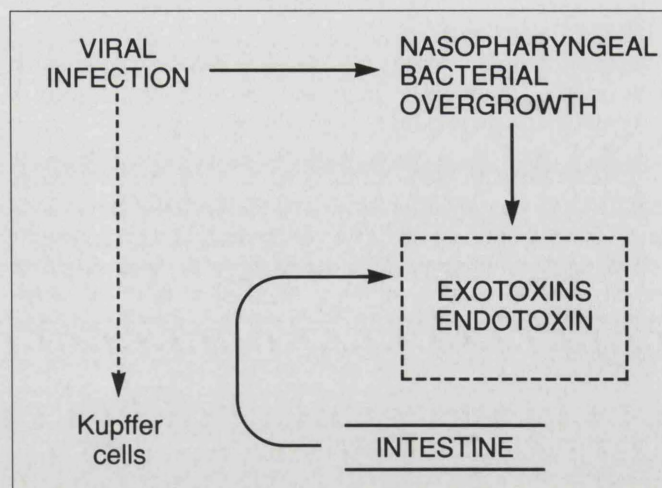


Fig 3 – The bacterial toxin hypothesis

Viral respiratory tract infections have a complex effect on the body. One of the consequences is that there is a disturbance of the normal nasopharyngeal bacterial flora leading to overgrowth of bacteria such as staphylococci, streptococci and enterobacteria. All these organisms are potentially toxigenic and it is inevitable that toxins will enter the circulation. In addition viral infections can disturb immunological responses. In certain cases Kupffer cell function in the liver is impaired and this can lead to endotoxin and exotoxin entering the systemic circulation from the gastrointestinal tract. Furthermore there is recent evidence that viruses and bacterial toxins can act in synergy to produce lethal effects in experimental animals.

The hypothesis is that viral respiratory infections will have these complex effects on infants, children and adults but it is only the infant, in the short period following the loss of material IgG, who is susceptible to the lethal action of bacterial toxins¹.

INVESTIGATING THE HYPOTHESIS

1 The nasopharyngeal bacterial flora in SIDS

The aim of the initial studies was to determine the composition of the nasopharyngeal bacteria flora in cases of SIDS and compare it to that of normal healthy infants at the same stage of development.

The cases of SIDS were examined as soon as possible after the death was discovered. In most cases the autopsy was performed on the same day but in a few cases it was delayed until the following day. The nasopharyngeal secretions were sampled by pernasal swabs which were passed prior to autopsy to reduce the possibility of secondary contamination. The swabs were plated on a wide range of standard microbiological media and incubated aerobically, anaerobically and in a CO₂ enriched atmosphere as required. All the colonial types which grew were identified, subcultured and recorded.

The comparison series consisted of pernasal swabs from normal healthy infants attending well baby clinics. Each SIDS case was matched with an infant of the same age (by months) and sex whose sample was obtained in the same month.

The final series consisted of 48 cases and 48 controls. The nasopharyngeal flora in the two groups was different³. There was increased carriage of staphylococci (41.3% versus 28.3%), streptococci (78.3% versus 32.6%) and enterobacteria (45.6% versus 2.2%) in SIDS cases compared with normal infants. The increased carriage of streptococci and enterobacteria was highly significant ($p < 0.0001$).

One obvious problem with this work is that the cases were sampled a few hours after death and the bacterial flora could have changed in this time. It was of interest, however, that the isolation rate of enterobacteria decreased with increasing time between death and sampling indicating that the high enterobacterial isolation rate was not due to post mortem overgrowth.

2 An animal model using gnotobiotic rats

The next stage of the investigation was to see if it was possible to produce an animal model of SIDS using gnotobiotic rats. These animals are reared under germ-free conditions in special incubators so that they have never encountered live bacteria. The idea was to challenge these rats with nasopharyngeal bacteria from SIDS cases thereby simulating the first encounter between bacteria and host which theoretically occurs in SIDS.

Initially bacteria were introduced to gnotobiotic rats by nasal insufflation. The rats were colonised by the bacteria but they did not suffer any harmful effects. Subsequently single bacterial isolates were injected subcutaneously. These injections caused a local reaction and some systemic disturbance but they did not cause rapid death. Finally combinations of bacteria were injected subcutaneously into gnotobiotic rats, in the same total dose as for single isolates. Some of these combinations, particularly *E coli* and *Staph. aureus*, did cause rapid death ie the injections were given in the afternoon and the rats were found dead the following morning. There were minimal histological changes at autopsy but live bacteria were isolated from rat tissues indicating that death was due to septicaemia not pure toxemia⁴.

Thus some, but not all, of the criteria for a model of SIDS were fulfilled. If the findings are relevant to SIDS they indicate that combinations of toxins acting in synergy, rather than single toxins, are important in SIDS. This helps to explain why SIDS is uncommon. All infants suffer episodes of viral infection and toxemia but only those with chance associations of toxins that are synergistic will be at risk of dying.

3 A chick embryo bio-assay system

The aim of the next phase was to develop a bio-assay system for lethal toxins using chick embryos. The nasopharyngeal bacterial isolates were grown on a cellophane membrane overlying blood agar. This membrane is semi-permeable, allowing low molecular weight nutrients from the agar to diffuse through to support surface growth, but retaining extracellular bacterial products over a molecular weight of 10,000 on the surface. The secretions were separated from live bacteria by washing the growth from the membrane, centrifuging it and finally filtering it. In this way a crude cell-free mixture of bacterial toxins was produced.

A small part of the mixture was then injected into the chorioallantoic vein of a ten to eleven day old chick embryo to assess lethality. This involved delicate manipulation of the embryonated eggs, the removal of a triangular piece of shell

using a dental drill (Fig 4), injection into the vein, closure of the defect using sellotape to prevent infection, incubation of the eggs for 36 hours and then assessment of viability of the embryos.

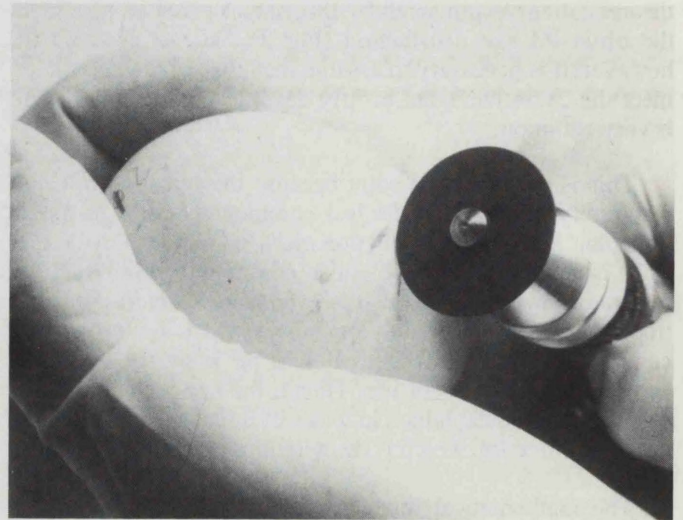


Fig 4 - A dental drill used to remove a triangular piece of shell from an embryonated egg.

Using this system we have shown that SIDS cases are more likely to harbour bacteria in the nasopharynx which produce lethal toxins than are normal healthy infants⁵.

4 Cellular localisation of bacterial toxins

To establish the hypothesis it will be necessary to demonstrate the presence of bacterial toxins in the blood and tissue of SIDS cases. The problem, however, is that the fatal level of toxin might be low and difficult to measure and it is possible that toxins could enter the circulation from the gastrointestinal tract at the time of death and confuse the findings. It would make the task easier if there were areas of the body where bacterial toxins are concentrated. With this in mind we have studied the fate of bacterial toxins injected intravenously into anaesthetised rats. The rat organs were removed and an immunohistological technique used to localise the injected toxins. With this experimental approach we have shown that staphylococcal toxins are concentrated in the proximal convoluted tubular cells of the kidney⁶ (Fig 5). It appears that the low molecular weight proteins are filtered by the glomerulus and then reabsorbed from the lumen of the

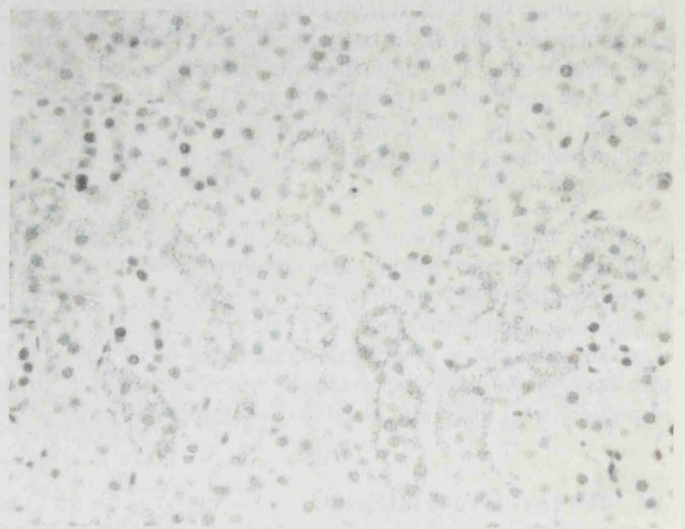


Fig 5 - Granular staining of TSSST in the proximal convoluted tubules of a rat kidney

proximal convoluted tubule. This is a normal route of protein reabsorption.

The next stage will be to prepare cell-free homogenates of kidney from SIDS cases and inject them into chick embryos to test for lethality. The appropriate controls will be kidney homogenates from cases of sudden traumatic death. If the SIDS kidney concentrates prove lethal this will be strong evidence in support of the toxin hypothesis. If they are not it will be equally strong evidence against it. These studies are now being planned and will be carried out in the Department of Biological Sciences at Lancaster University.

CONCLUSION

There is considerable evidence that infection is an important precipitating factor in many cases of SIDS. Neither viral infection alone nor bacterial infection alone can explain the full range of epidemiological features. But a two-stage model, as proposed above, in which viral infection leads to bacterial overgrowth and toxæmia, is consistent with all the epidemiological findings. More importantly the model is precise and is amenable to laboratory investigation. This work is now underway in Lancaster and in Manchester. The early results are encouraging but a great deal remains to be done.

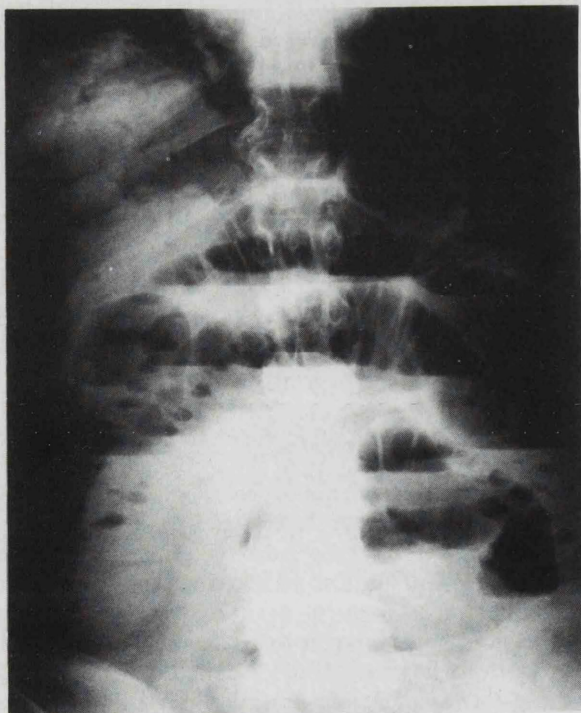
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QUIZ



What three abnormalities are present on this abdominal x-ray?

Answers on page 167