Review of the epidemiology of sudden infant death syndrome and its relationship to temperature regulation

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SUMMARY. Infants dying suddenly and unexpectedly now account for 20% of all infant deaths in England and Wales, and the incidence shows no sign of falling. Recent work relating sudden infant death to a raised environmental temperature and a raised body temperature, implicates fever as a possible contributory cause of death; some infants may be unable to control their febrile response to infection, or to thermoregulate effectively, when well wrapped and heated. Death might then result from apnoea, occurring in a critical sleep state.

These ideas have increased the interest in describing the normal practices of parents in caring for the environment of their infants in health and disease, and the effect of their behaviour on the child's temperature. Studies of these areas depend on collecting and interpreting data from young children during their day to day lives, and present a challenge of great relevance to primary care research.

Introduction

SUDDEN infant death syndrome is a mystery, as indicated by its definition: 'The sudden death of any infant or young child which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death'.[1] Epidemiological investigation of sudden infant death syndrome is beset by the problems of applying this definition and of making appropriate comparisons. The event is so rare that prospective studies must include 10 000 infants to obtain a mere 30 cases;[2] while retrospective studies relying on routinely collected data are unreliable because of the attention to clinical and pathological detail required to make a diagnosis of exclusion.[3,4]

Identification of specific risk factors for sudden infant death syndrome depends on a comparison of the characteristics of infants that die from the syndrome with those that do not from the same population at risk. The most appropriate controls might be accidental deaths in the same age group. Postmortem findings could then be compared and, as the tragedy surrounding both kinds of death is similar, recall bias would be minimized. However, accidental deaths are even more rare than deaths from sudden infant death syndrome and most studies have relied upon healthy infants as comparisons or have described uncontrolled findings. A further group much studied as living surrogates of sudden infant death syndrome are the 'near miss' group but these children are likely to include both normal infants and a specific group at risk of respiratory death and should not be uncritically accepted as representing infants at risk of sudden infant death syndrome.[5]

It is surprising that under these circumstances such a large body of basically consistent descriptive epidemiology has emerged over the last 20 years, along with some analytic studies, mainly of case control design.[6] It is perhaps less surprising that the proliferation of aetiological hypotheses for sudden infant death syndrome has easily outstripped the hard evidence and no convincing intervention studies have yet been carried out.

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Incidence of sudden infant death syndrome

In England and Wales babies who die suddenly or unexpectedly have only been identified as a group since 1971.[7] Since 1975, linkage of infant death with birth certificates has been available, with a link made for over 98% of deaths.[8] Since then, sudden infant death syndrome has become the most common recorded cause of death in the postneonatal period (28–364 days).[2] This is in part due to the sharp fall in deaths owing to infection and in part to changes in certification, as awareness of sudden infant death syndrome has grown. The increase in recording sudden infant death syndrome is thus paralleled by a reduction in certification of respiratory causes.[9,10]

A careful multicentre study of postneonatal deaths reported that for over 25% of routinely certified cases of sudden infant death syndrome, clinical or postmortem evidence of severe disease could be found.[4] However, on reappraisal, a similar proportion originally certified as dying from infection did not bear out this or any other diagnosis. Thus, the total number of deaths certified as sudden and unexpected is probably a fairly accurate reflection of the incidence of sudden infant death syndrome, but studies using routine statistics to identify risk factors for sudden infant death syndrome may misclassify risk factors for other postneonatal deaths.[9]

The suddent infant death rate in England and Wales was 1.95 per 1000 live births in 1984 (20.57% of all infant deaths)[11] and 2.24 per 1000 live births in 1987;[2] compared with other countries this is a relatively high rate. In comparing incidence rates in different countries there are problems of definition and ascertainment but there is a range from 0.3 per 1000 live births in Hong Kong and 0.9 per 1000 live births in Sweden to 6.3 per 1000 live births in southern New Zealand.[12]

Biological and environmental factors in causation

General risk profile

Neonatal (day one to 27) and postneonatal (day 28 to 364) mortality rates have shown contrasting secular trends in most developed countries. While neonatal mortality has shown a remarkable fall in the last 20 years, the rate of fall of postneonatal mortality has slowed over the same period, to the present rate of six per 1000 live births in England and Wales.[13] This is considered to reflect the greater effect of social rather than medical factors on postneonatal mortality rates;[9,11] thus mortality rates for this age group double between social classes 1 and 4, a greater variation with class than for any other age group.[14] A series of epidemiological surveys has confirmed that the risk profile for all postneonatal deaths is very similar to that for sudden infant death syndrome,[6,9] suggesting that social deprivation is also important in this sub-group.

The risk of sudden infant death is increased in social classes 4 and 5 and in cases of single parenthood or illegitimacy. It is also increased among younger mothers who have smoked or taken opiates or barbiturates in pregnancy, or received less ante-

natal care. The risk increases with the number of siblings, increasing birth order and a reduced birth interval and is more common among multiple births delivered pre-term or of low birth weight. Boys are more at risk than girls as are infants with congenital abnormalities.[6,9]

Studies involving careful necropsy have failed to find any consistent postmortem markers of sudden infant death syndrome[15] and there is good evidence against any mendelian inheritance of the condition.[10] Although some infants who die may have been less well than their peers in the days before death,[4] no evidence of specific prodromal illness exists.

Within the risk profile for sudden infant death syndrome the relative risks for each factor are in general only of the order of twice that in the comparison groups, reaching 3.5 or more only for maternal drug addiction, pre-term delivery or triplets.[6] Despite the multiplicative nature of relative risks, sudden infant death syndrome is so rare that the predictive power of scores based on risk factor analysis remains low for the individual child[15] and risk scores have not been recommended for general use.[4]

Age and season of death

Among the most intriguing epidemiological findings in relation to sudden infant death syndrome is the consistency of age and season of death. Throughout the world the majority of deaths occur when the child is between four and 20 weeks old with a peak incidence in the second and third month of life.[6,10,15] Similarly, in almost all large studies in both the northern and southern hemispheres there is a marked association with season, sudden infant death syndrome being more common in winter than in summer, even after the seasonal variation in birth rate has been allowed for.[6,15-19]

Many diseases of unknown aetiology undergo seasonal fluctuations,[20] but any hypothesis as to the causes of sudden infant death syndrome must explain the age distribution, the seasonal nature, and the deprived social and biological origins of many of the affected infants.

Causes and mechanisms

The most convincing explanation for sudden infant death syndrome is that of an infant dying at a period of increased physiological vulnerability when meeting some environmental hazard that would otherwise not prove fatal.

The physiological vulnerability may be predetermined *in utero*[21] but prospective studies of sudden infant death syndrome have so far failed to incriminate respiratory or cardiac pathophysiology in the neonate before death.[5,22] A recent report from Australia has demonstrated grossly raised levels of immunoglobins in the lungs of 16 victims of sudden infant death syndrome, compared with eight control infants dying from non-pulmonary causes.[23] This finding could reflect an unusual response to infection, and the seasonal nature of sudden infant death syndrome might implicate viral infection.[24,25] A highly significant correlation has been reported between the isolation of respiratory viruses in the general paediatric population and the rate of sudden infant death syndrome.[24] The failure to identify respiratory viruses in many victims of sudden infant death syndrome may prove to be a technical limitation of current diagnostic methods. An objection to the virus hypothesis is the failure to detect the expected space-time clustering of cases of sudden infant death syndrome.[6,17,25] Again, available methodology may not detect epidemicity, especially if several independent infective agents are at work,[25] or a combination of infection and other factors such as a problem with temperature control interact to result in sudden infant death syndrome.

The seasonal nature of sudden infant death syndrome also suggests a relationship with environmental temperature, and a recent study examined the relationship between the daily number of deaths ascribed to sudden infant death syndrome and daily temperature in England and Wales among the 6226 deaths occurring over the five year period 1979–83.[17] After filtering the data to remove the dominant seasonal trend and residual autocorrelation there remained a significant negative correlation between deaths and both the level and rate of change of temperature four to six days earlier. That any correlation between incidence of sudden infant death syndrome and temperature change was found is surprising given the problems with case definition in vital statistics and the crude measure of temperature used (outdoor temperature in central London was used for the whole of England and Wales). Other studies have also suggested a relation between sudden infant death syndrome and temperature, independent of viral infection.[19] However, the relationship between the trough in temperature and peak incidence of sudden infant death syndrome varies and no firm association with changes in the weather has been found in the days preceding cases of sudden infant death syndrome.[26]

The direct mechanisms that may link temperature change and sudden infant death syndrome range from hypothermia to hyperthermia. Mechanisms involving chilling include a direct physiological diving reflex or increased susceptibility to apnoeic attacks in the premature or developmentally sensitive infant in response to cold.[17,27] At the other extreme, Dallas first suggested that overheating might contribute to sudden infant death syndrome in 1974,[28] but presented no evidence. In 1979, five case histories were published of infants presenting in Newcastle over a three year period. Each infant had been unwell and left well wrapped up and was subsequently found shocked, convulsing and in all but one case died.[29] Four of the children had high temperatures (>40°C) and in all five, no other aetiological factor was found. A presumptive history of heat stroke was made.

Stanton has recently reviewed the evidence from further studies in Newcastle, East Germany, Sheffield, Belgium and South Australia.[30] It is clearly difficult to establish raised temperature as an antecedant of sudden infant death syndrome since the infants are often found hours after the event, and there is no specific postmortem marker of high temperature. The evidence is largely based on infants reported to be overdressed and hot and sweaty to the touch when found dead. In some cases the infant's room was hot and in others there was clinical or pathological evidence of infection. Among the cases of sudden infant death syndrome studied in the combined series,[30] 53% of infants were reported to have been drenched in sweat or with fevers above 37°C when found, often hours after last being seen alive. None of these studies were controlled, and there is little information on the temperature, sweatiness and clothing of infants in normal life.[31,32] It should also be borne in mind that a high temperature could be an associated and not causal finding in sudden infant death syndrome.

A plausible pathway for the contribution of fever to sudden infant death syndrome which explains the variation with season is that an infant at a vulnerable state of development is well wrapped and heated because of the cold outside or because of ill health, and is unable to control its febrile response to a viral infection or to thermoregulate in the face of the over-wrapping or a hot local environment. A recent thoughtful review from New Zealand emphasizes the importance of the head and face in thermoregulation of the well-wrapped infant.[12] The authors hypothesize that the prone sleeping position in infancy may compromise this route of thermoregulation and point to the low incidence of deaths from sudden infant death syndrome in Hong Kong where the supine position is traditional compared with the high and rising incidence of such deaths in New Zealand

where the prone position is more common.

The actual mechanism of death suggested[12] is that a combination of heat and infection could trigger febrile apnoea, particularly in the infant in a critical sleep state. A possible model has been found in the kitten which dies of febrile apnoea without specific postmortem signs.[33] The suggestion that such apnoea might be the younger infant's fatal equivalent of a febrile convulsion receives little support from the fact that the risk factor profile of the two phenomena are quite distinct.[6] Moreover, no relationship was found between the rates of hospital admissions for a first febrile convulsion over a five year period and the monthly rate of cases of sudden infant death syndrome.[34]

It is possible that in a small minority of cases an underlying muscle–membrane disorder predisposes to malignant hyperpyrexia as indicated in a recent case report[35] but the epidemiological significance of this finding remains to be explored, as do suggestions that pyrexia may facilitate endotoxin absorption.[36]

Future study

Further epidemiological study of the sudden infant death syndrome in different ethnic groups with different child rearing practices in hot and cold countries and in countries with and without variable seasons may help to unravel the effects of environment further; why for example is the rate of sudden infant death syndrome low in Sweden where infants are nursed in the prone position, and higher among Maori New Zealanders than Caucasian New Zealanders?[12] However, current epidemiological evidence points particularly to the need for further studies of developing infants when healthy and ill, in their normal environment and in the laboratory. The optimal thermal environment for a three month old infant when healthy and ill is not known, nor what are his or her parents' normal behavioural responses to temperature change in the environment or secondary to febrile illness.

While the physics and physiology of kittens and infants under laboratory conditions can examine the development and mechanisms of thermoregulation in the developing infant,[37] field studies of the diurnal temperature of infants when healthy and ill are essential to describe the range of temperatures usually experienced and their behavioural and environmental correlates. Recent work confirms the wide range of temperatures and wrapping within which normal three to four month old infants manage to thermoregulate.[32,38] In a series of 67 such infants monitored at home, the mean rectal temperature at bedtime was just over 37°C falling to 36.4°C within hours and then rising slowly towards dawn. No temperatures fell below 35.9°C while temperatures between 37°C and 38°C were not uncommon. This predictable pattern was found despite variations in room temperature from 22°C to 7°C and equally large variations in wrapping.[32,38]

Studies such as these require the application of both epidemiological and sociological methodology for success, as they need to collect and interpret data from the children and their environment during their day to day lives. They thus present a research challenge of great relevance to primary care.

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