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Sudden unexpected nocturnal deaths among Thai immigrant workers in Singapore

The possible role of toxigenic bacteria

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Summary. Sudden Unexpected Nocturnal Deaths (SUND) occur in young, apparently healthy immigrant workers from Thailand, the Philippines and Bangladesh living among ex-patriot labour forces in countries such as Singapore and Saudi Arabia. Several factors associated with these deaths are similar to those observed for Sudden Infant Death Syndrome (SIDS): sleep related and mainly noturnal occurrence; no prodromal illnesses other than mild respiratory tract infection; exposure to cigarette smoke; absence of invasive microorganisms at autopsy. The hypotheses proposed to explain these deaths in adults are examined. Based on our studies of the role toxigenic bacteria might play in some cases of SIDS, we suggest a new approach to the investigation of SUND.

Key words: Unexpected deaths – Toxins – SUND

Zusammenfassung. Plötzliche unerwartete nächtliche Todesfälle (SUND) ereignen sich bei jungen, offensichtlich gesunden Einwanderungs-Arbeitern aus Thailand, den Philippinen und aus Bangladesh, welche zwischen heimatlichen Arbeitskräften in Ländern wie Singapur und Saudi-Arabien leben. Mehrere Faktoren, welche mit diesen Todesfällen assoziiert sind, sind ähnlich zu jenen, welche für das Syndrom des plötzlichen Kindstodes (SIDS) beobachtet wurden: Beziehung zum Schlaf und im wesentlichen nächtliches Auftreten; keine prodromalen Erkrankungen, außer einer geringen Infektion des Respirationstrakts; Exposition zu Zigarettenrauch; Fehlen von invasiven Mikroorganismen bei der Obduktion. Die Hypothesen, welche vorgeschlagen wurden, um diese Todesfälle zu erklären, werden untersucht. Basierend auf unseren Untersuchungen über die Rolle, welche toxinproduzierende Bakterien in einigen SIDS-Fällen spielen könnten, schlagen wir eine neue Annäherung für die Untersuchung von SUND vor.

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Introduction

Sudden Unexpected/Unexplained Nocturnal Deaths (SUND) occur among immigrants from Thailand, the Philippines and Bangladesh working in countries such as Singapore and Saudi Arabia [1, 2] and also among southeast Asian refugees [3, 4]. In Singapore, the victims were usually employed in moderately heavy manual jobs such as labourers, construction workers, handymen or gardeners. Most of these deaths happen during the first year of residence in their adopted country [5].

There is an excess of young males (average age = 33) among SUND victims; only 5–10% are female. The majority of these deaths take place at night during the early hours of the morning or during an afternoon nap. Occasionally, the deaths have occurred in the evening when the person was engaged in conversation, playing an indoor game or watching television.

In Singapore, most of these deaths (88.9%) were among young men from provinces in northeast Thailand [5]. A recent survey by the Thai Public Health Service found that unexpected deaths among men between the ages of 20–59 was highest in the northeast provinces (32/100,000) compared with those in central (9.42/100,000), southern (18.26/100,000) or northern 20.9/100,000) provinces [Wichai and Sirisak, Thai Public Health Service, unpublished observations].

Hypotheses proposed to explain SUND

The epidemiological and pathological features of Sudden Unexpected/Unexplained Nocturnal Deaths (SUND) have stimulated a number of hypotheses as to their cause, however, as yet there is no satisfactory explanation for these deaths.

Autopsies have not been carried out on unexpected deaths in Thailand [Wichai and Sirisak, personal communication], but thorough investigations of these deaths in Singapore have found no evidence of a systemic allergic or hypersensitivity response. Toxicological studies have not demonstrated poisons in the body fluids or organs. The concentration of alcohol in the body fluids was nil or negligible [1, 5].

Ventricular fibrillation has been postulated as the ultimate cause of these deaths [6, 7]; however, detailed microscopy studies of the conduction system of the heart found no consistent abnormalities. Family studies of the siblings and other relatives failed to demonstrate any significant increase in the incidence of functional, conduction or other cardiac abnormalities [8].

Serological studies have not produced hard evidence for an infectious aetiology. In one series there was an increased incidence of antibodies to *Pseudomonas pseudomallei* [9]; however, this organism is endemic in southeast Asia and there is no relation between the classical pathology of disease due to this bacterium and SUND.

Low levels of potassium [10] and vitamin B deficiencies have been suggested to play a role in these deaths [11]. Studies on the diet of Laotian refugees among whom similar deaths occur did not substantiate the hypothesis, and the results could not account for the predominance of males among the victims as both men and women shared the same diet. The recent studies by Goh et al. [5] found no evidence to support this hypothesis.

Smoking and mental stress are suggested to be associated with SUND. Studies by the Thai Ministry of Public Health found a higher proportion of smokers (70%) among men who died unexpectedly in Thailand compared with the general population (50%) [Wichai and Sirisak, unpublished observations]. Smoking might also contribute to the predominance of males among SUND victims as smoking is more prevalent among Thai men (50%) compared with Thai women (< 10%).

A significant proportion of SUND cases and controls reported more emotional problems such as homesickness and anxiety over SUND while in Singapore but not in Thailand [5]. Mental stress is known to induce cadiac arrhythmias [12] and is associated with susceptibility to viral infections of the upper respiratory tract [13].

Parallels between SUND and Sudden Infant Death Syndrome (SIDS)

Our hypothesis that toxigenic bacteria might contribute to some cases of SUND has evolved from our studies of SIDS [14, 15]. Many cases of SUND and SIDS are sleep – related and occur mainly at night or during an afternoon nap. The absence of invasive microorganisms at autopsy and the absence of significant prodromal illness other than mild respiratory tract infection are common to both. A significant proportion of SUND victims were smokers or died in an environment in which they were passively exposed to cigarette smoke [3], and passive exposure to cigarettes smoke is significantly associated with SIDS [16]. In both SIDS and SUND there are the following non-specific clinicopathological findings: generalized congestion; subpleural petechiae; cerebraloedema; and empty bladder [17, 18].

Toxigenic bacteria, SIDS and SUND

Pyrogenic toxins

Strains of *Staphylococcus aureus* capable of producing pyrogenic toxins are often isolated from SIDS infants [19]. The pyrogenic toxins of staphylococci and *Streptococcus pyogenes* are powerful superantigens that have profound effects on the inflammatory responses of the host [20]. The pyrogenic toxins cause fever (> 38.5 C), are mitogenic for lymphocytes, induce release of tumor necrosis factor (TNF), interleukin 1 (IL-1) and possibly nitric oxide [21]. These toxins can also amplify the effects of endotoxic shock as much as 100,000-fold. The pyrogenic toxins are produced between 37°C–40°C and in greater quantities at the higher temperatures. If there are environmental factors that increase the temperature of individuals colonized with these toxigenic bacteria, this might significantly increase the amount of toxin produced by the bacteria. Death in either SIDS or SUND might be due to the sudden release of large amounts of inflammatory mediators.

Pertussin toxin

A second hypothesis is that some cases of SIDS or SUND might be due to asymptomatic infection by *Bordetella pertussis* [22]. Newborn infants are particulary susceptible to pertussis indicating that there is little protective antibody transferred from the mother. We have noted that in our area there has been a shift in the age range affected by SIDS. In 1988 < 20% of SIDS victims were </ 2 months of age. Since initiation of pertussis immunization at 2 months of age instead of 3 months, the proportion of SIDS infants </ 2 months of age has increased to > 40% [23]. Both the pertussis toxin and the staphylococcal enterotoxin B bind to the Lewis^a antigen on monocytes [21, 24]. We have suggested that the pertussis toxoid used to immunize infants might induce antibodies that are cross-reactive with the pyrogenic toxins and these antibodies partly neutralize their effects [23].

With respect to the second hypothesis, it is of interest to note that immunization against pertussis was not initiated in Thailand until 1978; therefore, a proportion of the

Table 1. Pertussis in the main regions of Thailand 1987–1992

Year	Region			
	NE	C	S	N
87	620	371	230	246
88	741	390	248	284
89	651	325	119	135
90	272	133	36	45
91	134	108	35	18

NE = northeast, C = central, S = south, N = north

immigrant workers might be susceptible to the toxin which can release insulin from pancreatic islet cells, and increases sensitivity to anaphylaxis or histamine. Epidemiological reports to the Thai Ministry of Public Health indicate that since 1987, nearly half the case of infection due to *B. pertussis* occurred in the northeastern provinces (Table 1).

Factors enhancing colonization by toxigenic bacteria

Infants

For infants, we have identified 2 factors that might enhance the probability of colonization or density of colonization by staphylococci and *B. pertussis*: expression of the Lewis^a antigen; and infection by respiratory viruses. The peak incidence of SIDS, occurs between 2–4 months. During this period 80–90% of infants express the Lewis^a antigen and *S. aureus* is isolated from approximately 40% infants in this age range [25]. We have demonstrated that the Lewis^a antigen is one of the receptors for 6 strains of staphylococci producing pyrogenic toxins A, B, C and TSST-1 and 2 non-toxigenic strains of staphylococci [15, 26]. Recently, we have isolated a protein adhesin that uses this host cell receptor from toxigenic staphylococci [27].

Our laboratory studies have demonstrated enhanced binding of staphylococci to HEp-2 cells infected with respiratory syncytial virus (RSV) [15]. *In vitro*, RSV infected cells express more Lewis^x antigen (structurally similar to Lewis^a) which we have also demonstrated to be a receptor for staphylococci and CD14 to which endotoxin binds [28, 29]. Binding of 2 strains of *B. pertussis* to epithelial cells was significantly inhibited by pretreatment of the cells with monoclonal Lewis^a or Lewis^x antibodies, and these bacteria bound in greater numbers to RSV infected cells [30].

Adults

In adults, factors associated with SUND that might enhance colonization or density of colonization by toxigenic bacteria are smoking, stress, expression of the Lewis^a antigen, exposure to new strains of respiratory viruses and lack of immunization to pertussis. Staphylococci bind in greater numbers to epithelial cells from smokers compared with non-smokers [31]. Smokers have more upper respiratory tract infections which have been found to enhance colonization by staphylococci [32]. Stress is associated with increased susceptibility to viral infection [13] and with increased cigarette consumption. Toxic shock syndrome has also been observed following influenza or influenza-like illnesses in adults [33].

Proposed sequence of events leading to SUND

SUND is probably multifactorial. The immigrants are under considerable stress adjusting to their new environment and working conditions. This increases cigarette consumption and, consequently, susceptibility to respiratory viruses in their new environment to which they have no specific immunity. Viral infections increase the probability of colonization or density of colonization by staphylococci or *B. pertussis*, perhaps due to increased amounts of Lewis^x or CD14 on epithelial cells. In the Thai population, the reported proportions of the non-secretor phenotype which predominantly express the Lewis^a antigen varied from 18–30% [34]. Studies are presently underway to determine if there are regional variations in expression of the non-secretor phenotype or expression of Lewis^a in the Thai population.

In the majority of individuals, colonization alone is probably not sufficient to initiate the series of events leading to SUND. As in the case of SIDS, additional environmental factors need to be considered, particularly those that might increase the temperature of the epithelial surface on which the toxigenic bacteria are growing [14]. If an individual is carrying bacteria capable of producing pyrogenic toxins and also develops a mild gastro-intestinal and/or respiratory tract infection, this might induce low grade fever and, subsequently, production of the toxin. More than 70% of SUND victims in the Singapore study had been self-medicated with both Thai and western medicines, mainly for headache and fever, and up to 24 hours before death, 41.7% complained of non-specific symptoms such as fever, headache, backache and loss of appetite [5].

Some deaths might be due to the synergistic effect of the pyrogenic toxin and small amounts of endotoxin from the gut resulting in induction of inflammatory mediators and in fatal shock. In the case of pertussis, death might be due to hyperinsulinaemia resulting from the action of the toxin on the islets.

In view of these findings and hypotheses, even if an autopsy cannot be carried out on SUND cases for social or religious reasons, if would useful to obtain the following specimens as soon as possible after death: nasopharyngeal swabs to be cultured for *B. pertussis* and *S. aureus;* a blood sample for determination of Lewis antigen phenotype and examination for exotoxins of pertussis and staphylococci and endotoxin levels. If it is possible to carry out even a limited autopsy, evidence for activation of the immune system should be sought by the appropriate immunohistochemical or other immunological techniques.

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