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Proposed link between *Helicobacter pylori* and sudden infant death syndrome

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Abstract — *Helicobacter pylori* may be linked to sudden infant death syndrome (SIDS) through synthesis of inflammatory cytokines, particularly interleukin-1, which can produce fever, activation of the immune system, and increased deep sleep. A relatively minor respiratory or enteric infection, together with overwrapping and prone sleep position could then induce terminal hypoxemia. Alternatively, *H. pylori* produces large amounts of urease which, if aspirated in gastric juice, could reach the alveolae, react with plasma urea, and produce ammonia toxicity leading to respiratory arrest. Epidemiological similarities between *H. pylori* and SIDS are presented along with possible transmission mechanisms for *H. pylori* which support this hypothesis.

Introduction

Sudden Infant Death Syndrome (SIDS) is a disease of antiquity, probably first mentioned as 'overlaying' in the Old Testament (I Kings 3:19); it is presently the major cause of postneonatal death in the industrialized world (1). The cause(s) of SIDS remains unknown despite intensive scientific inquiry. Although the prone sleeping position is the most powerful risk factor ever reported, it is not *the* cause of SIDS since infants dying of SIDS have died in other sleeping positions for years (2).

The five most significant postmortem findings in SIDS are: (a) no inherent lethal pathology; (b) evidence of mild infections, usually viral; (c) intrathoracic petechiae, patchy pulmonary edema, and emphysema; (d) histopathology suggesting pre-existing hypoxia: increased muscle mass in pulmonary arteries, extramedullary erythropoiesis, and increased adrenal brown fat; and (e) neuropathology: astroglial proliferation in brainstem, leukomalacia, and delayed loss of dendritic spines in reticular formation (3).

Helicobacter pylori is the most common chronic infectious disease in the world, affecting approximately 50% of its population (4). Infection is usually acquired in childhood, especially in those who are socioeconomically disadvantaged (5).

Proposed herein is a hypothesis which attempts to unify much of the current information related to the pathophysiology and epidemiology of SIDS by examining a possible link between *H. pylori* and SIDS.

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Risk factors

Infection

For many years, investigators have looked for an infectious cause of SIDS. Epidemiological factors associated with susceptibility to infections, especially those of the respiratory tract, are very similar to those associated with SIDS. Infants are particularly vulnerable to infection during the period when most SIDS occur (2–4 months) because their immune systems are immature. SIDS occurs more frequently during the winter months when there are more respiratory virus infections (6). Moreover, streptococci and Gram-negative bacteria that normally live in the gut have been isolated more frequently from the nose and throat of SIDS infants compared with healthy infants in the same age range (2 weeks to 6 months) (7).

Bottle feeding

Breast feeding protects infants from respiratory and gastrointestinal illnesses, and SIDS is associated more frequently with bottle feeding (8). Breast-feeding rates are also lower in low socioeconomic groups in which the incidence of SIDS is increased (9). Not breast feeding is associated with an odds ratio for SIDS of 2.93 (CI 1.84 to 4.67) (10). Breast feeding is not only protective, but the duration of breast feeding is also important; a progressively protective effect in a dose-response relationship has been noted for both black and white infants (11).

Maternal smoking

Smoking by the mother has been clearly identified as a risk factor for SIDS (10); children of smokers have more respiratory tract infections and could be at risk of acquiring bacteria carried in her nose and throat (12). There is a dose response relationship between maternal smoking and SIDS incidence (13). It has also been noted that as prone sleeping is reduced, the relative importance of smoking is increased (14).

Infection and immunity

Immunoglobulins and infection in SIDS have been studied with interesting results: SIDS victims have higher gamma globulin levels than does the normal population of the same age, suggesting a greater exposure to infections (15); lung immunoglobulins in lung lavage from SIDS infants compared with controls who died of nonpulmonary causes were found to be grossly elevated (16); and significant increases of IgG, IgM, and IgA-producing cells in tracheal mucosa, salivary glands, and duodenal mucosa were found in SIDS victims but not in controls, arousing speculation that interleukins or other cytokines might be involved (17,18). Interleukin-1 (IL-1), an endogenous pyrogen, has been proposed as a link between infection and prolonged sleep apnea leading to SIDS; IL-1 itself can produce fever, activation of the immune system, and increased deep sleep (19).

Hyperthermia

Hyperthermia has been implicated as a significant risk factor for SIDS; many SIDS victims have higher rectal temperatures, suggesting a febrile state prior to death which is consistent with the presence of an infection and/or overwrapping (20). In fact, it has been noted that the combination of infection-induced fever and excessive insulation (bedclothes) created an astounding odds ratio for SIDS of 51.5 (CI 5.64 to 471) compared with more lightly wrapped infants (21).

Sleep position

As noted, infant sleep position has been clearly linked to SIDS; by avoiding the once popular prone position through extensive public education efforts, SIDS rates have consistently and substantially dropped in surveillance reports throughout the world (22). Mechanisms for the dangerous effect of the prone sleeping position are not clearly defined but may result from reduced heat loss from the face (6), interference with air exchange (23), or interference with arousal or autoresuscitation in infants placed in this position (24).

Epidemiology of *H. pylori* and sudden infant death syndrome

Both of these diseases are more common in poor and non-white populations, in large families, in single parent families, in males, and in living situations where bed-sharing and overcrowding are common (23,25–29). Growth retardation has also been demonstrated for both SIDS victims (30) and children with *H. pylori* (28,31). Familial recurrence of SIDS is greater than in the normal population (32), and intrafamilial clustering of *H. pylori* has been documented (33). Although ELISA serology cannot be used to detect *H. pylori* in children less than 3 months old (passive maternal antibody transfer), studies using the ^{13}C-urea breath test have shown that at this age children may already be infected (34). In fact, in a

study in Peru, 71% of children aged 6 months were infected with *H. pylori* (25). In another study of an African-American population in the USA, prevalence conformed to an incidence of 3% yearly (5). In select high risk groups (such as SIDS familes), the incidence could be substantially higher.

How *H. pylori* explains sudden infant death syndrome

In human subjects, the incubation period of *H. pylori* from inoculation to clinical symptoms has been shown to be 3–7 days (35,36). Achlorhydria, with resulting possible enhanced infection risk from other organisms, may persist for 7–49 days (37). *H. pylori* infection in children is typically asymptomatic (38) but gastroesophageal reflux is more or less universal in infants, and, in the presence of *H. pylori* infection, may lead to repeated microaspiration, inducing subtle histologic changes in the upper airway and stimulation of immunoglobulins in the lung and gastrointestinal tract. In a recent study of aspiration pneumonia, *H. pylori* could be isolated in 10% of patients from tracheal aspirates (39). In addition, *H. pylori* produces large amounts of urease. It has been reported that intravenous administration of urease is fatal (40). This may have relevance to the immunologically naive individual (such as an infant) in which initial infection with *H. pylori* would result in gastric hypochlorhydria (35,36). As such, urease from *H. pylori* would be fully active and would be present in high concentrations in the neutral gastric juice (41). Therefore, pulmonary aspiration of such gastric juice could, in rare cases, cause large amounts of active gastric urease to reach the alveolae and thus be in close proximity to the plasma with its contained urea. Unlike the gastric mucosa, where urea hydrolysis is relatively harmless, urea hydrolysis in the lungs would produce ammonia in a less acid environment where it might remain in the un-ionized form. In addition, this ammonia would be supplied directly to the systemic circulation (pulmonary artery and aorta) where it could not be detoxified by the liver.

The absence of obvious lethal pathology in SIDS may relate to the failure to include microscopic findings of the gastric body or antrum as well as the difficulty in clearly visualizing *H. pylori* by standard hematoxylin and eosin staining of tracheal sections (42). Moreover, presence of ammonia in the blood of a recently deceased baby would not be unusual.

From an epidemiological standpoint, the similarities between SIDS and *H. pylori* infection are largely surrogate markers for low socioeconomic status; however, several features of SIDS could be explained by enhanced intrafamilial transmission of *H. pylori*. Because this organism has been found in dental plaque (43) and saliva (44) of infected individuals, maternal smoking (more frequent hand to mouth contact by the mother), salivary exposure from infected family members (particularly drooling by siblings), and handling (and using) potential fomites such as bottles and pacifiers by siblings must be considered in transmission of *H. pylori* to the neonate. A recent hypothesis has suggested that the natural route of transmission of *H. pylori* is by gastric juice, specifically as a result of epidemic vomiting in childhood (4). Sticky, mucousy vomitus which is difficult to clean up may be a suitable infecting medium, particularly in situations of overcrowding, where siblings share a bed, or in the absence of a fixed hot water supply. In addition, whatever the transmission mechanisms, regular handling of a newborn by siblings may be delayed for several weeks after birth, which, together with the apparent incubation period required for development of active gastric inflammation, might explain the absence of SIDS in the first month of life.

Human milk IgA against *H. pylori* can protect infants from early acquisition of infection (45). Breast feeding may also not only diminish risk of infection with other organisms associated with *H. pylori*-induced achlorhydria, but also would minimize exposures from a specific fomite (the bottle). Human milk also contains multiple nonantibody, antibacterial protective factors and anti-inflammatory agents; lysozyme, lactoperoxidase, and a receptor-like glycolipid or glycoprotein which inhibits bacterial adherence (a major factor in establishment of *H. pylori*) are examples of the former, while prostaglandins E2, F2a (cytoprotective), oligosaccharides (inhibits microbial attachment), and epithelial growth factors (strengthen mucosal barriers) are among the latter (9). Even in the presence of *H. pylori* infection, colostrum effects may dampen bacterial proliferation and inflammation, thus reducing cytokine production.

An appreciable number of immunological mediators are produced during *H. pylori* infection. These mediators elicit recruitment and activation of neutrophils or other inflammatory cells (IL-8) and modulate the immune or inflammatory response (IL-1, IL-3, IL-4, IL-6, IL-8, tumor necrosis factor-α [TNF-α], and interferon γ). Some of these mediators may be elicited by purified bacterial components such as porins (46–48). IL-1 is a highly inflammatory molecule and is synthesized in vascular tissue (49). It is possible that IL-1 plays a role in the petechiae formation characteristic of SIDS intrathoracic pathology. Moreover, IL-6 concentrations in cerebrospinal fluid

have been recently shown to be significantly higher in SIDS compared with violent death cases (50).

Since infants have low levels of specific immunity to microbial antigens during the age range in which SIDS occurs, the inflammatory response most likely is the key defense against a number of infectious agents. Cortisol has an important role in the inflammatory response by its ability to reduce capillary permeability and antibody synthesis, as well as to stabilize lysosomal membranes. Stimulation of the hypothalamus by cytokines such as IL-1, IL-2, IL-6, and TNF-α released from activated macrophages causes the secretion of corticotrophin-stimulating hormone and vasopressin which act on the pituitary to produce corticotrophin. These hormones act on the adrenal gland to stimulate cortisol (6); cortisol is increased in SIDS (51). However, control of the inflammatory response may be inadequate so that mediators with profound physiological effects are secreted by phagocytes and accumulate in higher levels, setting up a vicious cycle in the very young infant.

It is also clear that bacterial load is not the only potential determinant of mucosal injury and chronic inflammation; other variables include differences in host response (? effect of colostrum), bacterial strain, and perhaps environmental cofactors. Thus, not all *H. pylori*-infected infants would be expected to behave in a similar manner. Speculation exists that certain *H. pylori* strains harbor a virulence factor or factors which may predict development of peptic ulcer disease or gastric cancer.

Hypothesis

Once *H. pylori* has infected the neonate, vomiting or gastroesophageal reflux with microaspiration may occur leading to the immunologic and pathologic findings associated with SIDS. If large amounts of active gastric urease reach the alveolae, hydrolysis of plasma urea would produce ammonia supplied directly to the systemic circulation and lead to respiratory arrest from ammonia toxicity. In addition, gastric inflammation results in synthesis of the cytokine IL-1, with production of fever, activation of the immune system, and increased deep sleep. With the physiological effects of IL-1 in place, a relatively minor respiratory or enteric infection may then add to hyperthermia, with overwrapping or prone sleep position adding further burden and resulting in an acute, terminal hypoxemia. Pathologic findings reflecting prior hypoxic episodes could be explained by variations of these factors, or perhaps to a progressive inflammatory response to *H. pylori*.

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