Overview of Investigations into Pulmonary Hemorrhage among Infants in Cleveland, Ohio

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Idiopathic pulmonary hemorrhage was diagnosed in 37 infants in the Cleveland, Ohio, area between 1993 and 1998. This rare disorder has been related to 12 deaths, including 7 originally thought to be sudden infant death syndrome. Thirty of the infants were African American, all of whom lived in a limited geographic area of eastern metropolitan Cleveland, an area of older housing stock. An investigation led by the Centers for Disease Control and Prevention has found an association with household exposure to a toxigenic mold, Stachybotrys chartarum, and other fungi. The rapidly growing lungs of young infants appear to be especially vulnerable to the toxins made by toxigenic molds. Environmental tobacco smoke was frequently present in the infants' homes and may be a trigger precipitating the acute bleeding. Stachybotrys, although not thought to be a common mold, is known to have a wide geographic distribution. An additional 101 cases of acute, idiopathic pulmonary hemorrhage have been reported in infants in the United States over the past 5 years. In this overview, the investigations are summarized, the clinical profile is described, the toxicity of S. chartarum is discussed, and pathophysiologic concepts are presented.

Key words: environmental tobacco smoke, idiopathic pulmonary hemosiderosis, indoor mold, pulmonary hemorrhage, satratoxins, Stachybotrys chartarum, sudden infant death syndrome, toxigenic fungi, trichotheceans. — Environ Health Perspect 107(suppl 3):495-499 (1999).

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Background

Between 1993 and 1998, 37 cases of pulmonary hemorrhage and hemosiderosis have been identified in young infants in the vicinity of Cleveland, Ohio. Twelve of the infants have died. In November 1994, the Centers for Disease Control and Prevention (CDC) began an investigation to determine the cause of this outbreak (1,2). Thirty of these cases have occurred within a contiguous nine zip code area in the eastern part of the metropolitan area. The case–control study found an association with home water damage (3) and the presence of the toxigenic fungus Stachybotrys chartarum and other fungi in indoor air. This fungus was found in higher quantity in the air of the home environments of the affected infants but also at a lesser degree in some of the comparison homes (4). Stachybotrys requires water-soaked cellulose to grow, and was found in homes where there had been water damage from flooding, plumbing leaks, or roof leaks involving wood or paper products (e.g., insulation, gypsum board, ceiling tile). The spores of this fungus contain very potent mycotoxins capable of producing acute toxicity. Secondary stresses, e.g., environmental tobacco smoke, appear to be important triggers of overt hemorrhage. Since the initial investigation, additional cases have occurred in Cleveland infants. The clinical spectrum of this disease varies from overt, life-threatening hemorrhage to very subtle initial symptoms such as nose bleeds and chest congestion. Concern that there may be a larger number of undetected young infants with this disorder led to the examination of all infant coroner cases over the past 4 years. This revealed seven sudden infant death syndrome cases with major amounts of pulmonary hemosiderin-laden macrophages, indicating extensive hemosiderosis existing prior to death. All but one of these infants had lived in the same geographic cluster area in Cleveland.

This problem may extend beyond Cleveland, as toxigenic fungi are widespread and chronic water damage is common in poorly maintained homes throughout the nation. Informal surveillance (5) has identified 138 infants with idiopathic pulmonary hemorrhage in the United States during the past 5 years. The following is an overview of the clinical features of the Cleveland infants with pulmonary hemorrhage, the results of the field studies, the toxicity of S. chartarum, and working concepts of the pathogenic mechanisms.

Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (PH) is a rare disorder, especially in infants. Over the 10 years prior to 1993, there had only been three pediatric cases with this disorder at Rainbow Babies and Childrens Hospital, a referral center for all of northeastern Ohio. The incidence of PH in Sweden is 2.4 per 105 children per year (6) and in Japan it is 1.1 per 105 children per year (7). Within the limited geographic cluster area, the Cleveland incidence for 1993–1995 was 1.5 per 1,000 live births. Immune disorders are the most common etiology of PH in adolescents and adults (e.g., Goodpasture's, systemic lupus erythematosus) but are unlikely to occur in infants and have never been reported in children less than 2 years of age. An association of PH in infants and young children with elevated IgG precipitins against cow milk proteins (Heiner's syndrome) (8) has been specifically excluded in this cluster of Cleveland cases (3). Other causes of PH, such as cardiac structural disorders giving increased pulmonary venous pressure, have also been excluded. In contrast to adult PH, the majority of PH in infants and children is idiopathic (9). A retrospective study of 30 childhood cases over 20 years in Greece (10) speculated the possible role of pesticides; other toxicants have been implicated in older patients (11).

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Isolated acute pulmonary hemorrhage in infants is probably more frequent than hemosiderosis and can arise from multiple causes (e.g., necrotizing pneumonia, trauma) (12), but prolonged bleeding does not occur in these cases. Hemosiderosis, defined as alveolar and/or interstitial distribution of hemosiderin-laden macrophages, occurring beyond the acute hemorrhagic period is evidence for a chronic bleeding process. Human and animal studies indicate that hemosiderin-laden macrophages are cleared from the alveoli in about 2 weeks (13,14). Thus, to classify a patient as having hemosiderosis beyond the repair period of the acute hemorrhage, bronchoscopy for bronchoalveolar lavage (BAL) should be performed more than 3 weeks after the initial bleed. The finding of large quantities of hemosiderin-laden macrophages in these BALs defines these patients as having ongoing bleeding, i.e., hemosiderosis, and not just isolated hemorrhage.

**Investigation of Pulmonary Hemosiderosis in Cleveland**

The initial investigation directed by the CDC focused on the first 10 cases and 30 age- and geographic-matched control infants (3,4). All cases were African American, 9 were male, and none had been breast-fed. Sixty percent of the cases experienced recurrent pulmonary hemorrhage upon returning to their homes. (Subsequently, only 12% of patients kept out of their original home environment have had overt rebleeding.) A 240-item questionnaire followed by extensive home environmental surveillance and testing revealed to reveal pesticide exposure or other potentially related household toxic substances (3). However, the case infants’ home environments had a higher prevalence of water damage (odds ratio [OR] = 16.25; 95% confidence interval [CI] 2.55–∞) and a higher quantity of airborne S. chartarum (OR = 9.83; 95% CI 1.08–3 × 10⁶)(4). Other, non-specific molds, which may include some toxigenic species, were also significantly increased as a group in the case homes. Although Aspergillus, Cladosporium, and Penicillium were abundant in the case infants’ homes, matched analyses for these molds failed to demonstrate differences in concentrations between case and control homes. Because raw sewage was the source of water damage in only one case home, Gram-negative bacteria and endotoxins were not investigated. Multivariate matched analysis implicated exposure to environmental tobacco smoke as a risk factor in the presence of S. chartarum (OR = 21; 95% CI 1.07–7.5 × 10⁶). The study concluded that infants with pulmonary hemorrhage and hemosiderosis were more likely than controls to live in homes with toxigenic S. chartarum and other fungi in the indoor air (4).

While 16 of the 28 control homes investigated had some evidence of S. chartarum, continued study of subsequent cases showed 20 of 23 tested case homes were positive. Subsequent analysis of the Cleveland mold isolates has confirmed their ability to produce several macrocyclic trichothecene toxins, including satratoxins G and H (15). Neither the cytotoxicity or mycotoxin content of extracts from the cultured isolates statistically distinguished between the case and control homes (15). Mold samples taken directly from the homes have not been analyzed for mycotoxins. A highly sensitive assay capable of detecting trichothecene toxicity in airborne particulates has been developed for use in subsequent investigations (16). Further etiologic correlations will require the development of analytical techniques capable of demonstrating the fungal toxins in blood and/or urine samples from these infants and the reproduction of the disorder in infant animals, both of which are goals of ongoing research.

Why the cluster of cases occurred in a limited geographic area of Cleveland is unclear. This is a residential area of primarily wood frame homes, most of which are more than 60 years old and may be inadequately maintained (3). The area is a drainage plain where basements are frequently flooded in heavy rainstorms. The forced air heating in these homes commonly draws air from the entire basement, providing a means for airborne particulates to be circulated up into the infants’ sleeping areas. Based on the 1990 census (17), the area contains 20% of the county population, 82.2% of the population is African American, 48.2% of all the children live below the poverty level, and 38.0% of these children live with a single, unemployed parent.

**Clinical Profile of Cleveland Cases**

This cluster of cases in Cleveland has been limited to infants, all but two of whom have been <6 months of age (mean age at initial hemorrhage = 3.1 months). Most of the 30 patients (excluding the seven cases diagnosed postmortem) have presented with respiratory distress (88%) requiring intensive care (81%), often needing ventilator support (73%), usually for several days, and blood transfusions (50%). Seven patients developed respiratory failure prior to any overt signs of hemorrhage, which became apparent only upon intubation. Few of these infants were experiencing clinical events associated with stresses that usually do not produce respiratory failure, e.g., anesthesia induction for elective surgery, hypernatremic dehydration, water intoxication, and febrile seizures. At least four infants had overt pulmonary hemorrhage associated with apparent upper airway obstruction (neck flexion in car seats), and one patient had a subsequent fatal hemorrhage while sleeping prone with her blanket pulled into her face. Nonpulmonary manifestations have included neurologic problems (11% with developmental delay and/or failure to thrive, 22% with seizures), concomitant infection (19%, including Pneumocystis carinii pneumonia), and hemolysin with hemoglobinuria (26%). All of the patients available for subsequent bronchoscopy (22 patients) have had continued hemosiderosis, most for >6 months. During this period of chronic bleeding, 21 patients have been treated with steroids (prednisone: 1.0 mg/kg/day) for an average of 8.7 months, although the role of inflammation in these infants is not well established. Three of the five patient deaths occurred without the use of steroids or after stopping them before the hemosiderosis had completely resolved. Additional therapy for reactive airways was required for 39% of the infants for 3–6 months following the pulmonary hemorrhage. This is twice the incidence of respiratory illness with wheezing in normal infants (18).

**Toxicogenic Fungus**

Stachybotrys chartarum (Ehrenb. ex Link) Hughes (= Stachybotrys atrah Corda) (19) is one of several environmental fungi that produce very potent compounds toxic to humans and animals. The symptoms of farmworkers exposed to the agriculturally important fungi are well described and for S. chartarum include nasal and tracheal bleeding (in contrast to the alveolar bleeding discussed above), skin irritation, and alterations in white blood cell counts (20–22). Both toxic and inflammatory mechanisms appear to be involved. S. chartarum produces satratoxin G and H and roirdin, the most potent members of a large family of trichothecenes.
Mouse Inhalation Studies

Acute and subacute inhalation studies using intranasal instillation of *S. chartarum* spores with 5-week-old adult mice have been reported. In the acute study (45), mice were exposed to 10⁶ spores containing satratoxin G and H or to the same dose of spores from a strain that produced undetectable levels of these trichothecenes but comparable levels of the phenylspirodri-manes. The mice receiving the toxic spores developed severe alveolar, bronchial, and interstitial inflammation (neutrophils, macrophages, lymphocytes) with luminal hemorrhagic exudates, whereas the spores without satratoxins induced a much milder inflammation. In the subacute studies, biweekly intranasal administration for 3 weeks (46) produced similar dosage-dependent inflammation using 10³ and 10⁵ toxic spores, significantly milder inflammation with 10⁴ nontoxic spores, and no inflammation with 10⁶ nontoxic spores. These numbers of spores are reasonable given the inefficiency of inhalation from nasal instillation and because 6.3 × 10⁴ colony-forming units/m³ of *S. chartarum* were found in the bedroom of one of the Cleveland infants. All of the mice failed to develop IgG antibodies to *S. chartarum*. This is not surprising for those receiving the toxic spores, as trichothecenes are known to kill macrophages ingesting the spores (47) and even humans who become ill after exposure to *S. chartarum* often do not develop IgG or IgE anti-Stachybotrys antibodies (38–40). The pulmonary inflammation seen with spore inhalation is in contrast to previous studies (48) with aerosolized solutions of trichothecenes. The latter produced no respiratory tract inflammation; rather, cell necrosis and lysis were seen in spleen, thymus, and intestines. Because the latter organs were spared in the spore studies, it appears that the fungal spores may be slow-release reservoirs that tend to limit the toxic effects to the more immediate locale. There are no reports in the literature of studies with toxic spores or trichothecene solutions administered by inhalation or by ingestion to infant animals of any species.

Pathophysiologic Concepts

In view of the clinical profile of the disorder in young infants and the knowledge about the toxic actions of *S. chartarum* toxins, the following pathogenesis is suggested. The disorder appears to be associated with the inhalation of *S. chartarum* spores containing toxins, most notably the trichothecene protein synthesis inhibitors, satratoxins G and H, or rosidin E (15). Because young infant lungs are growing very rapidly, protein synthesis of type IV collagen and other endothelial basement membrane components would be particularly sensitive to inhibition. Thus, the release of these toxins could lead to focal areas of capillary fragility. Subsequent exposure to stresses that alter blood flow in the lungs (e.g., unequal hypoxic vasconstriction from environmental tobacco smoke, marked sympathetic reaction to asphyxia) could lead to local areas of increased capillary pressure and subsequent stress hemorrhage of these fragile capillaries. Transmural pressures insufficient to rupture normal capillaries may be pathogenic under these conditions (49).

There are several possible explanations for the hemosiderosis that persists for months beyond the acute hemorrhagic period. The capillaries may remain fragile for a prolonged time with an increased susceptibility to leakage even with comparatively minor stresses. The mouse studies found a severe inflammatory reaction persists beyond an acute toxicity period. This inflammation could be a source of alveolar bleeding, either directly or through interaction with any persisting capillary fragility. The nonpulmonary manifestations are similar to those described in animals exposed to *S. chartarum* and are consistent with the immune suppressive, neurotoxic, and hemolytic effects of the trichothecenes and/or accompanying mycotoxins. One patient in Cleveland had accompanying *P. carinii* pneumonia and a transitory but severe suppression of his T-cell mitogenic response to concanavalin A and phytohemagglutinin consistent with exposure to cyclosporin. The stachytoxins may contribute directly to the hemorrhage by antagonizing the vasoactive properties of endothelin-1, a paracrine hormone released by endothelial cells in response to hypoxia (50).

Summary

An epidemiologic investigation of pulmonary hemorrhage in infants in Cleveland found an association with exposure to *S. chartarum* and other airborne fungi. Exposure to environmental tobacco smoke was an additional risk factor in the presence of *S. chartarum*. Further studies are needed to determine whether the fungal association is causal. Logical pathophysiologic concepts do
derive from a comparison of the clinical profile of these infants and the known actions of mycotoxins from *S. chartarum*, notably the trichothecenes satratoxins G and H. Sufficient association and rationale exist to institute public health prevention measures as indicated in recent recommendations from the American Academy of Pediatrics (17). Prevention has begun in the Cleveland cluster area. It appears that this is a newly recognized disorder that is a subset of idiopathic pulmonary hemorrhagic disorder.

**Recommendations**

The home environments of infants with idiopathic pulmonary hemorrhage should be investigated for water damage and toxigenic fungi. Such infants should be excluded from environments containing toxigenic fungi and from environmental tobacco smoke, as the latter appears to be a trigger of acute hemorrhage in these infants. Conditions of chronic water incursion into residential structures needs to be avoided, flooding should be cleaned up quickly and adequately prior to reoccupancy, and cellulose materials should be removed from any area that is frequently wet. Infants who die suddenly without known cause should have an autopsy that includes a Prussian blue stain of lung tissue to look for prior pulmonary hemorrhage as indicated by the presence of hemosiderin.

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