Objective: An overview of the pathophysiology of viral upper respiratory tract infection and their Clinical implications.

**VIRAL UPPER RESPIRATORY INFECTION**

Viral respiratory tract infections are the most common illnesses affecting children. The reported incidence of upper respiratory infection is 24% for all children less than 5 years of age.

Several studies have attempted to standardize upper respiratory infection symptoms in an effort to distinguish patients with upper respiratory tract infections. In general, most clinical studies require the presence of at least two of the following criteria: sore or scratchy throat, sneezing, rhinorrhea, congestion, malaise nonproductive cough, fever (mild), or laryngitis. Only a few studies have utilized viral studies to definitively determine the presence of a viral infection. However, the anesthesiologist in the usual clinical setting will not have the advantages of time and viral studies to determine the presence of a viral URI. This empiric definition of upper respiratory infection is not only helpful in clinical studies but is relevant in clinical practice where viral cultures will not be available.

**CLINICAL STUDIES --CONFLICTING REPORTS**

Remarkably little data exists to establish the type and extent of morbidity that may occur when a child with a recent or current-URI undergoes general anesthesia. In 1977, Koka, et al. suggested that postintubation croup was not more likely to occur in a child with a recent or existing URI. In 1979, McGill et al. described a series of cases in which eleven asymptomatic patients with a history of recent upper respiratory infection during the month prior to surgery developed significant pulmonary infiltrates or atelectasis which was associated with an alveolar-arterial oxygen gradient of more than 30 torr.

DeSoto, et al, studied 25 children from ages 1-4 years with signs and symptoms of URI undergoing myringotomy, adenoidectomy and/or tonsillectomy and compared oxygen saturation while in the recovery room to healthy age-matched controls. This study suggested that a significant amount of pulmonary dysfunction, as seen by the lower oxygen saturation values, does occur in patients with a URI who undergo general anesthesia and surgery, although no morbidity was noted.

Tait, et al, reviewed retrospectively 3,585 patients aged newborn to 20 years to assess intraoperative complications in patients with URI. Interestingly Tait found that patients with a recent history of a URI had a significantly increased risk, for the development of the intraoperative pulmonary complications of laryngospasm, bronchospasm, stridor, or breath-holding. Patients with a current URI were at no increased risk of intraoperative complications.

Tait and Knight proceeded to do a prospective cohort study of 489 pediatric patients undergoing myringotomy under general anesthesia via face mask. Viral cultures were done and viral isolates included rhinovirus, respiratory syncytial virus, parainfluenza, enterovirus, and herpesvirus. When compared to normal healthy patients, there was no significant difference in perioperative complications in patient with positive viral cultures. Tait concludes that there is no increased morbidity for children with upper respiratory infection who undergo simple procedures under general anesthesia and who are not intubated.

Additionally, Tait found that respiratory symptoms in the patients with a URI who underwent anesthesia and surgery were less common and of significantly shorter duration. Although controversial, Tait suggested that perhaps the anesthetic agent, halothane, might alter the virulence of the virus and actually decrease the symptomatology of the URI. In animal studies, Tait has shown no increase in respiratory morbidity when anesthesia is administered to influenza-infected ferrets. However no decrease in symptoms in anesthetized versus non-anesthetized infected ferrets was seen.

Cohen and Cameron used a large previously collected database to evaluate the additional risk imposed by a URI occurring in a child undergoing anesthesia and surgery. The anesthetic records of 1283 children with a preoperative URI as defined as an “upper respiratory problem” were reviewed and compared with children without any “preoperative medical conditions.” These authors found that children with a URI were at a significantly higher risk for a respiratory-related event in the intraoperative recovery room, and postoperative time periods. Intubation, whether or not the patient has a URI, appeared to be a significant factor for the development of an adverse respiratory event. Although the authors suggest that the age of the patient should be a consideration in determining whether or not to proceed with surgery in a patient with a URI, this study did not determine a consistently higher respiratory risk in any single age group. The risk of postoperative croup in a child less than one year of age with a current URI was higher than other age groups and, also, higher than infants who did not have a URI.

Schreiner, et al, in a prospective case-controlled study of 615 patients report a 2.05 greater incidence of laryngospasm in children with URI as defined by their parents. The occurrence of laryngospasm was not related to URI as defined by the Tait and Knights criteria nor to history of recent URI’s. The results of this study demonstrate both an increased risk of anesthetizing children with URI’s and the difficulty of establishing criteria for assessing this condition.
Upper respiratory infections are the most common illnesses affecting children less than 5 years of age in the developed world and are a significant cause of childhood morbidity. Children under one year of age have an average of 6.1 respiratory illnesses per year and children between the ages of 1 and 5 have an average of 4.7 to 5.7 respiratory illnesses per year. Twenty-four percent of the children surveyed in the Atlanta metropolitan area had an upper respiratory infection during the two weeks before the interview. Children attending day care appeared to be more likely than children who did not attend to have a recent upper respiratory infection (32% of attendees v 21% of non-attendees). With the present high use of daily child care outside of the home, it seems likely that many children with a recent or current history of URI will present for elective surgery.

A wide selection of viruses causes rhinorrhea and upper respiratory infection in children. Rhinoviruses, parainfluenza viruses and influenza viruses are the most common viruses causing respiratory illness. The type of virus most commonly causing URI varies with different age groups. Respiratory syncytial virus, parainfluenza viruses, adenovirus are the most common viruses infecting the infant and preschool child. Rhinovirus and Mycoplasma pneumoniae predominate in the school-age child and adolescent.

Many effects of viral respiratory infections on the upper and lower respiratory systems have been described. Viral infections which appear clinically to be restricted to the upper airway may and usually do affect the lower airway causing small airway dysfunction and bronchial hyperreactivity. Viral upper respiratory infections are associated with ciliary abnormalities interfering with normal mucociliary clearance which last between two and ten weeks following the resolution of the infection clinically. Abnormal pulmonary function tests including decreased FVC, FEVI, peak expiratory flow rates, and maximal midexpiratory flow are found in children with URI’s. This small airway dysfunction may last for weeks following the clinical infection.

Bronchial hyperreactivity associated with URI has been studied quite extensively, especially in conjunction with the role of URI in the provocation of asthma. Viral URIs will initiate wheezing more commonly in children than adults, whether or not they have a history of asthma. Factors that predispose patients to develop airway hyperreactivity during viral URI’s are (1) children younger than 5 years of age, (2) family background of allergic disease, (3) if the infecting respiratory microorganisms are respiratory syncytial virus, parainfluenza rhinovirus, influenza, or M. pneumonia, (4) the coexistence of symptoms with the respiratory viral infection; for example, malaise, rhinorrhea, and increased mucus production, (5) male subjects and (6) preexisting airway hyperreactivity. It is interesting to note that bacterial respiratory infections of the lower airways do not appear to play a large role in provoking airway reactivity. However, bacterial sinusitis does cause wheezing in some patients with asthma.

PATHOPHYSIOLOGICAL CHANGES

The changes in lung function seen during and after a viral respiratory infection, are thought to be a result of airway inflammation and epithelial damage. The exact mechanism of pathogenesis of these changes is not known but is commonly thought to be a complex interaction of the specific immunologic systems in the lung with large roles played by the autonomic nervous system, IgE hypersensitivity, and immune mediators.

AUTONOMIC SYSTEM DYSFUNCTION--CHOLINERGIC

It is well established that the principle autonomic input to airway smooth muscle is via the parasympathetic cholinergic vagus nerve. Airway smooth muscle is apparently not affected directly by respiratory viruses since isolated infected airway smooth muscle has been found to have a normal contractile response to acetylcholine. However, when the vagus nerve is severed in parainfluenza infected guinea pigs and the distal end of the vagus nerve is electrically stimulated, the degree of airway contraction is exaggerated when compared to normals. Also, in the same virus infected model but with an intact vagus nerve, there is enhanced airway responsiveness to inhaled histamine. Both the afferent and efferent limbs of the vagus appear involved in the development of airway hyperreactivity seen in viral infections.

Busse suggests that (1) respiratory viruses injure airway epithelium and sensitive afferent, rapidly adapting, sensory fibers to promote vagus mediated reflex bronchospasmsm then (2) efferent vagal contractile activity is also enhanced. The enhanced efferent activity of the vagus must be due to increased amount of acetylcholine released from the vagus, since acetylcholine, as Buckner demonstrated, will initiate only a normal contractile response infected animals. Fryer et al demonstrated that parainfluenza virus infection damages inhibitory M2 muscarinic receptors located on the vagal nerve. These receptors are involved in a negative feedback loop by inhibiting the further release of acetylcholine when stimulated during the release of acetylcholine from the vagus nerve. When blocked or damaged by a viral infection, these receptors will result in larger amounts of acetylcholine released from the vagus nerve to be active in airway contraction. The viral enzyme neuraminidase may be responsible for the damage to the M2 muscarinic receptors causing the increased activity of the efferent limb of the vagus nerve.

Many other mechanisms have been postulated as responsible for modulation of acetylcholine output from nerve terminals, including neuropeptides, histamine and prostaglandins.

AUTONOMIC SYSTEM DYSFUNCTION--ADRENERGIC

Respiratory viruses are thought to decrease adrenergic function in the airway smooth muscle. Leukocytes are used to evaluate autonomic nervous system function in asthma. Granulocytes incubated with rhinovirus or influenza virus demonstrate a diminished response to isoproterenol (decreased generation of cyclic AMP, less inhibition of lysosomal release) when compared to normal granulocytes. Respiratory infection may selectively cause a blockade of adrenergic inhibition of bronchial smooth muscle contraction. The mechanism is not known.
IgE ANTIBODY

It has long been known that asthma is strongly associated with immediate hypersensitivity and IgE antibodies. Respiratory viruses stimulate IgE antibody production. In children less than 1 year old with respiratory syncytial virus or parainfluenza, Welliver et al, found that patients with wheezing or croup during the infection developed significantly higher levels of IgE specific antibody and greater concentrations. Additionally, infants with high respiratory syncytial virus IgE titers had much more chance of developing subsequent wheezing episodes when followed prospectively for four years. It is suspected that virus specific IgE antibodies are mast cell bound, interact with a respiratory virus antigen, and cause release of vasoactive and inflammatory agents, in turn, causing bronchial and epithelial damage. Ultimately, this results in airway hyperreactivity.

NEUROPEPTIDES

Neural control of the airways is very complex and includes, among other mechanisms, non-adrenergic, non-cholinergic mechanisms involving neuropeptides such as vasoactive intestinal peptide, substance P and other tachykinins. Substance P is located in unmyelinated sensory nerves (C-fibers) and has an inflammatory effect on smooth muscle from the trachea to the small bronchioles. In addition, substance P also stimulates airway mucus secretion, increases airway microvasculature permeability and degranulates mast cells. Substance P may be the excitatory neurotransmitter for noncholinergic bronchoconstrictor nerves. The major metabolizing enzyme, neutral endopeptidase, is localized in the epithelium of the airway. Viral infection causes a 50% decrease in airway neutral endopeptidase activity resulting in large amounts of unmetabolized tachykinins. This increase in available tachykinins causes pronounced effects on bronchoconstriction, microvascular leakage, and mucous production.

PHYSIOLOGICAL CHANGES WITH ANESTHESIA AND URI

Dueck et al, studied the effects on FRC and gas exchange measurements of anesthetizing six sheep before and after a parainfluenza-3 viral infection. Anesthesia produced an increased intrapulmonary shunt lower PaO2 and higher pulmonary arterial pressure. This viral infection involved the lower respiratory tract as evidenced by necrosis and sloughing of epithelial cells in the terminal airways and necrosis of alveolar epithelium. Although it is not possible to entirely extrapolate these data to infants and children with upper respiratory tract infections, this information does suggest significant pulmonary compromise during anesthesia with viral respiratory infection.

THE FUTURE

Specific agents to treat the effects of viral damage to the airway are being developed. M3 antagonists, which would block the effect of increased available acetylcholine without blocking the inhibitory M2 receptors are being tested but are not available for humans at this time. All anticholinergics currently available block both the M2 and M3 receptors.

Recombinant neutral endopeptidase has been used to replenish the neutral endopeptidase lost by epithelial damage by viral infection. In animal trials, coughing produced by substance P was decreased for 2 hours after the administration of neutral endopeptidase. Additionally, corticosteroids may stimulate the production of neutral endopeptidase.

In summary, viruses are frequent pathogens in childhood respiratory disease. Although there are indications from clinical studies and there is information regarding the pathophysiology of viral respiratory infections suggesting that viral URI's may be a source of perioperative morbidity, there are currently no prospective randomized studies to document significant danger to the patient. If there are no signs of overt viremia, bacteremia or lower respiratory infection and the surgery is not cancelled, anesthesia may be undertaken keeping in mind the possible complications which can be encountered, such as bronchospasm, laryngospasm, croup or atelectasis. Avoid intubation whenever possible, consider early use of atropine, and be prepared to treat bronchospasm. Continued study of the pathophysiology of viral respiratory infection will lead to further specific therapies for the child with a URI undergoing general anesthesia.

REFERENCES


