Immotile Cilia Syndrome

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Immotility of the cilia in the respiratory tract has recently been described in individuals with chronic respiratory disease. Changes in the normal configuration of cilia are observable at the ultrastructural level by electron microscopy. In patients with Kartagener's syndrome (situs inversus, bronchiectasis, and sinusitis), there is a defect in mucociliary transport owing to functionally ineffective ciliary movement which has been called "immotile cilia" syndrome or, as suggested more recently, "dyskinetic cilia" syndrome. The dynein arms, which are normally found attached to the microtubular doublets, are absent or deficient (short "spur"). Dynein arms contain the ciliary adenosine triphosphatase protein dynein. Adenosine triphosphate induces active sliding of adjacent microtubular doublets resulting in ciliary movement. Other abnormalities described in patients with immotile cilia syndrome include absence of radial spokes even in the presence of dynein arms, transposition of ciliary microtubules, and loss of parallelism of the plane of arrangement of the central pairs of microtubules in adjacent cilia (normally within 25°).

Ciliated epithelia are present in the respiratory tract, the paranasal sinuses, the eustachian tubes, the ependyma lining of the ventricles of the brain and spinal cord, and the oviducts. Human sperm tails are modified cilia with identical ultrastructure and are subject to the same ciliary deficiencies. When occurring in sperm tails, sterility has been noted, but no sterility problems have been noted in women with the same cilia defects. Kartagener's syndrome appears to be of autosomal recessive inheritance. It is assumed that during early embryonic life, ciliary beats in the growing embryo determine the type of laterality. When ciliary movements are absent, laterality may develop fortuitously, thus affecting a situs inversus in about half the affected individuals.

Recurrent episodes of bronchitis with segmental atelectasis, sinusitis, nasal polyposis, otitis, and mastoiditis have all been noted in individuals with immotile cilia. The lining of the bronchial tree and nasopharynx with its communicating chambers (sinuses and middle ears) are normally covered with a fine carpet of mucus. This mucus is swept along by ciliary movement of the pharynx, then swallowed or expelled. Defective ciliary movement or dysfunction is seen in the absence of significant defects in immunoglobulins, complement, phagocytic granulocytes, and alveolar macrophages associated with recurrent and chronic infection.

Laboratory Studies

Children with histories of recurrent bronchitis, sinusitis, polyps, otitis media, and in some cases of bronchiectasis in which immunologic studies have been found to be normal, should be investigated for ciliary abnormalities. Immunologic studies should include evaluation of immunoglobulins, both quantitatively and qualitatively, assessment of the cellular immune system, complement screening, and evaluation of the phagocytic system. In some individuals, allergy evaluation is appropriate.

Nasal and bronchial biopsies and, in some instances, biopsies of the middle ear and sinus areas can be performed to demonstrate ciliary abnormalities. With a curette, biopsies of the mucosa of the inferior and middle conchae may be taken and examined within a few minutes by phase contrast microscopy. The nasal mucosa may show only a few areas with recognizable cilia, and no motile cilia may be seen. Electron microscopy studies of biopsies of ciliated respiratory mucosa (or sperm samples) can provide confirmation of the diagnosis of immotile cilia syndrome, but an adequate sample is necessary. Between 50 and 100 cilia with proper orientation in cross-sectioned profile should be studied before a diagnosis of immotile cilia syndrome is rendered. Dynein arms may not be visible on all of the outer doublets of normal cilia because of variations in orientation and fixation. Other ultrastructural findings may include cilia with multiple axonemes; an addition, deletion, or disorientation of an outer doublet; and ballooning of the outer ciliary membrane. However, these have not been shown to be diagnostic for immotile cilia syndrome.

Differential Diagnosis

The immotile cilia syndrome should be considered in the differential diagnosis of children with chronic upper and lower respiratory infections. Chronic bronchitis and bronchiectasis, although disruptive to respiratory epithelia, do not alter normal ciliary beating and function.

Mucociliary dysfunction can be seen in asthma. Tracheobronchial secretions may be difficult to expectorate and may contribute to bronchial obstruction. Impairment of mucociliary transport mechanisms have been noted, but the pathogenesis is still poorly understood. Elaboration of chemical mediators in the lungs seems to depress mucociliary function. The clinical pattern of acute bronchospasm should be helpful clinically, and ciliary ultrastructure will be found to be normal by electron microscopy.

Patients with cystic fibrosis have normal mucociliary clearance and ciliary ultrastructure. These patients tend to have more severe bronchial obstruction than patients with immotile cilia and have more discomfort from chronic rhinitis, sinusitis, and otitis media.

Various immunologic abnormalities must be carefully excluded by appropriate studies. Children with cellular immune abnormalities, complement defects, and phagocytic defects will also present differential diagnostic problems comparable to patients with immotile cilia.

Therapy

Since children with immotile cilia have difficulty with mucociliary transport and clearance, efforts can be made to help them clear their respiratory mucosa. Postural drainage and physical therapy may be helpful to prevent pooling of secretions. This should be attempted three or four times per day during episodes of lower respiratory tract infections. Administration of a bronchodilator prior to postural drainage probably will be of little benefit since bronchospasm is not a primary feature of this syndrome. On the other hand, when there is combined nonallergic asthma or even significant change in pulmonary function with bronchodilators, it can be helpful to maintain the individual on therapeutic levels of theophylline.

Since motile cilia are a primary defense mechanism in the sinuses, chronic sinusitis is likely to develop. The lower respiratory tract will tend to have chronic retention of mucus and inhaled material causing bronchi to dilate to a bronchiectatic condition. Preventive measures should include immunization against respiratory pathogens such as *Bordetella pertussis*, rubeola, influenza, and *Streptococcus pneumoniae*. Early detection of bacterial infection by culture must be available. Appropriate antibiotic therapy is, of course, indicated on an intermittent or even at times on a daily basis. Chronic sinusitis and bronchiectasis may require continual antibiotic therapy, rotating antibiotics to avoid the emergence of resistant organisms. Usually, antibiotics that are effective against Haemophilus species as well as pneumococci, including amoxicillin, ampicillin, or a combination of trimethoprim and sulfamethoxazole or cefaclor, are effective. Recurrent respiratory infections tend to cause these children to lose many days of school and separate them from their peers, resulting in significant educational and developmental problems. Ciliary immotility is compatible with a fairly normal life and in this age of antibiotics with a fairly normal life span. It will, however, likely lead to chronic bronchitis and eventually to obstructive changes in the airways.