

Dyskinetic Cilia and Kartagener's Syndrome

Bronchiectasis with a Twist

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Introduction

Kartagener's published description of the syndrome of sinusitis, bronchiectasis, and situs inversus achieved eponymous recognition for him (1), although the clinical features had apparently been described previously by Siewert (2). A familial tendency was noted in some subsequent cases, and it was concluded that the condition was probably hereditary.

In 1975, Camner et al. (2) reported immotile respiratory cilia and immotile spermatozoa in two patients with Kartagener's syndrome. They suggested that the basis for the chronic sinusitis, bronchial infections, and bronchiectasis was impaired ciliary clearance of mucus due to the immotility of the respiratory cilia. Subsequent studies have shown that a variety of ciliary morphologic defects and abnormalities are detectable by electron microscopy and are accompanied by absence of motility in the cilia (4). The term "immotile cilia syndrome" was proposed for such cases (5). As many of these patients did not have situs inversus, it was concluded that Kartagener's syndrome is a subgroup or variant of the immotile cilia syndrome.

It is now recognized that the anatomically abnormal cilia are not always immobile, although the movement, when present, is dysfunctional, dyskinetic, and ineffective. The terms "dyskinetic cilia syndrome" (DCS) and primary ciliary dyskinesia are now applied to this syndrome. The latter term is pertinent because anatomic abnormalities in the respiratory cilia may also be secondary to pre-existing destruc-

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tive bronchial disease, and therefore not necessarily a manifestation of hereditary DCS.

Etiology and Pathogenesis

DCS is considered to be an autosomal recessive disorder. The incidence has been estimated to be between 1 in 12,500 to 1 in 40,000, although it is apparently most common in Japan (6). Genomic studies strongly suggest locus heterogeneity (7)

Situs inversus is present in about half of cases of DCS. The mechanism for the occurrence of Kartagener's syndrome is poorly understood.

The most likely explanation is that normal ciliary function in the embryonal archenteron determines the usual left-right asymmetry of the internal organs (situs solitus). Conversely, the absence of ciliary function presumably results in random left-right asymmetry, which could explain the presence of situs inversus in about half the cases (8). Noone et al. (9) reported a set of monozygotic twins with DCS; one had situs solitus and the other showed situs inversus totalis, which supports the concept that the situs status is random and not genetic. In cases of DCS, heterotaxy (deviation from situs solitus) may be incomplete (situs ambiguus) or complete reversal of normal organ position (situs inversus totalis) (10).

Other congenital abnormalities have occasionally been noted in cases of DCS. These include Marfan syndrome, polysplenia, hepatic steatosis, hydrocephalus, and Usher's syndrome (2).

Clinical Manifestations

The mechanism of the disease manifestations in patients with DCS is a profound decrease in mucociliary clearance in the upper and lower respiratory tracts. The accumulation of mucus predisposes to recurrent infections, primarily bacterial. Despite the widespread bronchiectasis, severe diffuse airflow obstruction is not usually a prominent feature.

The typical clinical pattern in DCS begins with recurrent upper respiratory infections with the onset in infancy or early childhood. These respond relatively well to antibiotic therapy, but in time acute and chronic sinusitis, otitis media, and recurrent lower respiratory infections become increasingly apparent manifestations.

Bronchiectasis eventually develops, and is accompanied by chronic production of purulent sputum, with episodes of pneumonia or hemoptysis in many instances. Situs inversus is present in approx 50% of cases. Sterility is present in most males due to loss of spermatozoal motility, although in some cases, the spermatozoa are structurally and functionally normal (11).

Tests for DCS

Pathological demonstration of the typical ciliary abnormalities by electron microscopy is the most specific feature of DCS, but adequate specimens must be obtained and handled properly (12). Nasal mucosa is the most easily accessible tissue for biopsy. DCS must be differentiated from the ciliary anatomical abnormalities that may occur in smokers and with chronic bronchitis, influenza, and other viral infections, and occasionally in normal individuals without bronchial disease (2).

Impaired mucociliary clearance can be assessed by measurements of nasal taste transit time (saccharin test), which is relatively simple and noninvasive (13). Ciliary beat frequency and the presence of abnormal wave forms can be studied by scintigraphic methods (12).

Diagnosis and Differential Diagnosis

The clinical picture in DCS patients is highly suggestive of the disease. The diagnosis should be considered in all patients with chronic rhinitis, sinusitis, otitis media, and chronic bronchiectasis, irrespective of the presence of situs inversus. Diseases that mimic DCS in some respects include respiratory allergy, cystic fibrosis (CF), immune disorders, and alpha-1-trypsin deficiency (14).

Confirmation of the diagnosis is most reliably established by detection of the characteristic anatomic abnormalities by electron microscopic examination of biopsies of bronchial or nasal mucosa. Sometimes the abnormality is subtle, particularly if ciliary malorientation is the only manifestation (12).

Measurements of mucociliary clearance for the diagnosis of DCS have high sensitivity but lower specificity; false-positives may occur with asthma, bronchiectasis, chronic bronchitis, CF, and some acute respiratory infections (15). Nevertheless, it is an excellent screening test.

Treatment

Although DCS is not curable at the present time, patients with this disorder often had a relatively long life span even in the pre-antibiotic era. The useful therapeutic tools currently available include careful and scientific use of antibiotic therapy, and a variety of techniques to enhance the ability of patients to clear mucus from the upper and lower respiratory tracts. It is also quite apparent that the benefits of therapy are enhanced by early diagnosis and prompt vigorous application of the therapeutic techniques.

New Horizons

The phenotypic heterogeneity of DCS syndromes is exemplified by recent reports. Eight individuals with all of the classical features of Kartagener's syndrome were shown to have membranous bronchiolitis in addition to bronchiectasis, pansinusitis, and situs inversus (16). As membranous bronchiolitis occurs in Japan in individuals without Kartagener's syndrome, the concomitant presence of the two conditions may be purely coincidental.

Severe bronchiectasis in four patients with a ciliary abnormality characterized by "cystlike" structures within the ciliary shafts has been recently described (17). There were measurable defects in mucociliary function as measured by the saccharin test. As the ciliary anatomy was otherwise normal, and the patients did not have sinusitis, it is probable that this is not a form of DCS.

Nasal-Bronchial Relationships in DCS

As in the case of CF, the nasal and bronchial manifestations of DCS are virtually identical in mechanism and similar in clinical manifestations. The basic underlying mechanism is mucociliary dysfunction in the nasal/sinus and bronchial mucosa, and the clinical manifestations are recurrent infections due to excessive mucus accumulation (15). Nasal infections result in pansinusitis and otitis media; bronchial infections eventually result in bronchiectasis in most instances. As previously noted, diffuse airway obstruction is a relatively minor manifestation.

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