**The United Airway — Allergy and Beyond**

Adele Pentz, MB ChB, DCH(SA), FC Paed(SA), MMed, Dip Allergol (SA)

Teshni Moodley, MB ChB, FC Paed(SA), MMed, Dip Allergol (SA), Cert Pulm(Paed)(SA)

Robin J Green, PhD

Department of Paediatrics and Child Health, University of Pretoria, South Africa

**ABSTRACT**

The concept of a ‘united airway’ became popular to link allergic rhinitis and asthma in many individuals who had symptoms of both upper and lower airway disease. Because of the common epithelium that runs all the way down the airway it is not surprising that in many individuals allergens trigger inflammation in both sites. However, the mere fact that some individuals have both symptoms of rhinitis and lower airway pathology does not mean the condition has an atopic basis.

Since the airway has a limited number of ways of expressing symptoms, namely runny, sneezy, itchy and blocked nose, as well as cough or wheeze, these symptoms may also be produced in individuals who have quite a long list of other disease states. Although these are less common, healthcare workers will have to consider at some time that symptoms may be from primary ciliary dyskinesia, immune deficiency (primary or secondary), cystic fibrosis, Samter’s triad or even recurrent viral airway infections.

This article explores these conditions, suggesting their pathophysiology and symptom base. A clear message, to think of one of these conditions if symptoms do not have an allergy base and do not respond to first-line therapy, is expressed.

**INTRODUCTION**

Within allergy circles the idea of the ‘united airway’ has become popular to managing patients who have a combination of allergic rhinitis (AR) and asthma. Indeed it has been claimed by some authors that all asthmatics have some degree of upper airway disease, and that management of that component of their problem eases the severity and cost of asthma. Upper airway disease in this syndrome includes AR but also sinusitis and middle ear disease.

However, all too often, patients with a variety of other conditions have both upper and lower airway symptoms and present exactly as though allergic. Proof of allergy is not present and while these conditions are less common, they may be missed if a practitioner does not keep an open mind to their possibility.

Conditions that may produce a united airway syndrome include:

- Primary ciliary dyskinesia (PCD)
- Primary immunodeficiency (PID)
- Acquired immunodeficiency (HIV)
- Cystic fibrosis (CF)
- Samter’s triad
- Recurrent viral infections of the airway.

This article provides some information about the diagnostic characteristics of each of these syndromes but is light on suggestions for management strategies to improve their burden on patients’ quality of life.

**WHY A LINK BETWEEN THE UPPER AND LOWER AIRWAY?**

The short answer to this question relates to the fact that the airway is continuously lined by the same epithelial structure from just inside the nose down to the terminal bronchioles. This is a ciliated pseudostratified columnar epithelium. That it is one long continuous surface makes it logical that pathological and inflammatory processes might affect many parts of this chain.

**The atopic link**

Both asthma and AR are defined as inflammatory conditions. The epidemiological relationship between upper and lower airway disease (rhinitis and asthma) demonstrates that 58-78% of asthmatics also have AR. Asthma occurs in up to 38% of individuals with AR. Many surveys have documented a rising prevalence of both these conditions. Childhood asthma and AR are two of the commonest chronic conditions in developed communities and they occur together in many patients.

The important link between upper and lower airway disease seems to be through a common pathology which affects similar epithelial structures, and the inflammatory process is the common factor where upper and lower airway diseases coexist. Clinically it has been noted that rhinitis and asthma are temporally related. Studies with large numbers of patients, both adult and child, have documented rhinitis beginning soon before or at the same time as asthma in 49-64% of patients. It may be that rhinitis is a marker for more severe asthma, or alternatively, that as inflammatory airway disease increases in severity, more sites of disease will be involved.

Lastly, the association between upper and lower airway disease can be found in the response to therapy. Improvement in asthma symptoms have been demonstrated in patients with both AR and asthma, treated only with topical nasal steroids during the ragweed pollen season. Topical nasal therapy does not enter the lung, and direct therapeutic effect is limited to the upper airway; consequently this pulmonary effect must either be through a neural mechanism or, more likely, by modification of the generalised inflammatory cytokine response. Appropriate therapy of one or both conditions in developed communities and they occur together in many patients.

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- Cystic fibrosis (CF)
- Samter’s triad
- Recurrent viral infections of the airway.
and poorer symptom control, which may increase medical resource use. A study of patients with asthma alone compared with patients with both conditions found differences in terms of unscheduled or specialist visits and hospitalisations. Presence of self-reported concomitant AR in patients with asthma resulted in a higher rate of asthma attacks and more emergency room visits compared with asthma patients without concomitant AR.13

PRIMARY CILIARY DYSKINESIA (PCD)

Since the airways are lined with functional cilia that aid in removing foreign material, any defect in the mucociliary escalator may produce both upper and lower airways symptoms. A congenitally determined abnormality in cilia is termed PCD.

This clinical syndrome was initially described by Kartagener in the 1930s as a triad of situs inversus, chronic sinusitis and bronchiectasis.14 Several decades later patients with this syndrome were found to have ultrastructural defects in the organisation of cilia. Initially the term immotile cilia syndrome was used (but the cilia are often motile although their beat is uncoordinated and ineffective). The name was then changed to primary ciliary dyskinesia.

Ciliary structure and function

The large airways, nasal passages, paranasal sinuses and middle ear are lined by ciliated, pseudostratified columnar epithelium (Fig. 1), important for mucociliary clearance. Mature respiratory ciliated cells contain approximately 200 cilia of uniform size with an average length of 6 μm and a diameter of 0.2 μm. Ciliary motion takes place in two phases: an effective stroke phase sweeping forward and a recovery phase during which the cilia bend ‘backward’. During the stroke phase the cilia make contact with mucus, propelling it forward, and during the recovery phase contact with the mucus is lost as the cilia extend into the starting position for the stroke phase.15

Each cilium has an array of longitudinal microtubules arranged as 9 doublets formed in an outer circle around a central pair (Fig. 2). Cross section of the cilia reveals inner and outer dynein arms attached to each microtubular doublet. Normal human cilia bend in a rapid, rhythmic, wave-like motion. Ciliary beat frequency is faster in the proximal airways than in the distal airways (12 beats/sec in the nose and trachea v. 8 beats/sec in the bronchioles) and is faster in children than in adults (13 beats/sec v. 11 beats/sec). Ciliary motility is maintained in the same plane along the length of the airways (because of parallel orientation of the central pair of tubules in adjacent cilia (Fig. 3)). Mucociliary transport rates may be as rapid as 20-30 mm/min.15

A large number of abnormalities have been documented in cilia that may result in this condition (Table I).

### Table I. Ultrastructural defects in PCD

<table>
<thead>
<tr>
<th>Dynein arm defects</th>
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<tr>
<td>Total or partial absence of inner and outer dynein arms</td>
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<tr>
<td>Total or partial absence of inner dynein arms</td>
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<tr>
<td>Total or partial absence of outer dynein arms</td>
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<tr>
<td>Shortening of dynein arms</td>
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<tr>
<th>Radial spoke defects</th>
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<tr>
<td>Total absence of radial spokes</td>
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<tr>
<td>Absence of radial spoke heads</td>
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<tr>
<th>Microtubular disposition</th>
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<tr>
<td>Absence of central pair of tubules with transposition of outer doublet to the centre</td>
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<th>Other</th>
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<tr>
<td>Ciliary disorientation</td>
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<td>Ciliary aplasia</td>
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<td>Absence of nexin links</td>
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<tr>
<td>Basal body anomalies</td>
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<tr>
<td>Central microtubular agenesis</td>
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<td>Normal ultrastructure but impaired function</td>
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Nose and paranasal sinus involvement in PCD
Nasal congestion is often present since early infancy, with little or no seasonal variation. Parents will often give a history of nasal symptoms within the first week of life, often from the first day. Most patients describe a chronic mucopurulent nasal discharge. Sinus X-rays or computed tomograms (CTs) demonstrate mucosal clouding, thickening and/or opacification. Nasal polyps occur in one-third of patients. Anosmia, hyponasal speech and halitosis may occur in severely affected patients.16

Lung involvement in PCD
Children often present with difficult-to-control asthma and may have a dry or productive cough. Bronchiectasis often follows at an older age.

PRIMARY IMMUNODEFICIENCY (PID)
Primary immunodeficiency often results in recurrent respiratory tract infections; we are just beginning to understand the many levels of immune dysregulation that can give rise to infections.

Table II lists the warning signs that suggest a patient should be worked up for PID. These alerting signs of PIDs, based on expert opinion, have been published widely by many organisations and publications and they have no doubt helped identify thousands of patients. However there is little published literature on the comprehensive awareness for and effectiveness of these criteria in different regions of the world. In South Africa specifically it is important where and at whom the awareness education should be targeted so that we do not miss the patient with PID. In regions with high prevalence of infectious diseases, the death of an infant or complications of infections such as bronchiectasis can all too easily be ascribed to the infectious organisms, while the underlying cause may be missed. Consanguinity is more prevalent in North African countries and the South African Asian population as a cause for severe combined immunodeficiency (SCID) with excess of autosomal recessive inherited disorders, but family history is one of the single most important features in early diagnosis of PID overall. In South Africa like in other countries where BCG vaccine is given routinely at birth, the dissemination of BCG in the HIV-negative infant is an early and serious warning sign of severe immunodeficiency.

The various types and investigations for PID have been nicely reviewed in an article by Professor Monica Esser in the November 2012 issue of this journal.17

CYSTIC FIBROSIS (CF)
Cystic fibrosis is a genetic disease with an autosomal recessive inheritance pattern. The identified gene was named the cystic fibrosis transmembrane conductance regulator (CFTR) gene.18 CF is caused by the reduction or dysfunction of the CFTR gene leading to abnormal transport of chloride and sodium across epithelial membranes involving the whole respiratory system as well as other systems.

Upper respiratory tract symptoms are not uncommon in CF individuals. Nasal polyposis is but an end of the spectrum of this disorder. However, clinicians running CF clinics will attest to frequent rhinitic symptoms, including a blocked nose, in most patients with CF. They frequently require topical nasal steroids in addition to all the therapies that are given for lung disease.

Upper respiratory tract symptoms begin in infancy and are frequently non-specific. Early recurrent wheezing and cough in a child who has associated gastrointestinal symptoms and growth failure should alert a clinician to the possibility of CF.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)-ASSOCIATED DISEASE
In the same way that PID may produce recurrent infections, so acquired immune deficiency may produce a similar trend if the condition is left untreated. HIV-infected individuals get more frequent ‘colds’ as well as lower respiratory tract infections. Viruses as well as bacteria may be responsible. In addition the bacterial organisms causing disease tend to be more antimicrobial resistant and this may necessitate attention to high-dose broad-spectrum penicillins and addition of clavulanic acid.

Table II. Warning signs that suggest PID

1. >4 new ear infections within 1 year: this may not be an uncommon feature in infants who are placed in crowded day or home care and in those where atopy is not managed optimally
2. >2 serious sinus infections within 1 year: the access to health care and correct use of antibiotics have to be taken into account in disadvantaged communities at risk
3. >2 months of oral antibiotic treatment with little effect: risk factors mentioned under (1) and (2) have to be taken into account here, as well as the indiscriminate use of antibiotics, and the patient history of a frequent change of doctors or clinics where a dedicated primary doctor is not part of the healthcare structure
4. >2 episodes of pneumonia within 1 year: this in the absence of predisposing risk factors such as foreign bodies, cystic fibrosis and respiratory complications after birth in the absence of HIV can be an important alerting sign
5. Failure of an infant to gain weight or grow normally: this, although a very important sign, may not become a feature until later in infancy even in SCID
6. Recurrent, deep-skin or organ abscesses: impetigo and superficial abscesses in the absence of an identified PID are not uncommon in the lower socioeconomic environment patient or with neglected or severe eczema. A hepatic abscess however, especially with granuloma formation where acid-fast bacilli cannot be isolated should immediately alert to PID related to neutrophil dysfunction, in particular chronic granulomatous disease (CGD).
7. Persistent thrush in the mouth or fungal infections of the skin.
8. Need for intravenous antibiotics to clear infections: this has been identified as one of the 3 key alerting signs for PID especially relating to neutrophil defects.
9. >2 deep-seated infections, including septicaemias: children or adults presenting with recurrent meningococcal disease in South Africa especially in the Cape regions should be investigated for complement deficiencies at least with the cost-effective total complement assay.
10. A family history of PID: this is the single most important feature in early identification of patients with PID especially in those (but not only) with recurrent or severe infections. Congential anomalies may further alert to the presence of PID, e.g. in the case of DiGeorge syndrome.
SAMPER’S TRIAD
In individuals with aspirin hypersensitivity symptoms are produced in the airway in all regions. Samper’s triad comprises:
• Asthma
• Nasal polyposis
• Aspirin hypersensitivity.
This condition may not be as uncommon as thought and should be considered in patients with atypical asthma who also have nasal polyposis.

RECURRENT VIRAL INFECTIONS OF THE AIRWAY
It has been suggested that a normal child may have up to 12 upper respiratory tract infections in a year (see article by Abbott in this issue). It is also known that in infants and young children many of these translate into recurrent lower respiratory tract infections, especially wheeze. This means that many young children may have frequent upper and lower respiratory tract symptoms. These resemble the symptoms of the atopic child but may not be allergic in origin. In fact viral-induced airway disease is more common than atopy.

CONCLUSION
Because of the common epithelial lining of the airway and probably because it is the first line of defense of the body against environmental insults, symptoms in many patients are frequently present in both the upper and lower airway. In addition because the human respiratory tract has a limited number of ways of responding to challenges, these symptoms are often common to a number of different underlying pathologies. In the upper respiratory tract runny nose, sneezing and a blocked nose may occur and in the lower respiratory tract cough and wheeze are present.

This article has suggested that both normal children and those with more severe problems are troubled by recurrent upper and lower respiratory tract symptoms. Therefore all that must be remembered is that when a child has atypical symptoms or unusual associated symptoms, it may be time to reconsider your primary diagnosis. Although it may be prudent to think first that a child with recurrent rhinitis and cough or wheeze has no more than viral infections, allergy and atopy may be your next thought, but if the problem is not solved, or if there are any of the associated problems listed here, it is time to think beyond viral disease or atopy.

Declaration of conflict of Interest
RG declares:
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REFERENCES