Clinical review

Fortnightly review

Seasonal allergic rhinitis

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Seasonal allergic rhinitis or hay fever was called "catarrhus aestivus" (spring catarrh) in 19th century medical literature, but more recently has been labelled as a "post industrial revolution epidemic."[1] Its prevalence has increased in developed countries, particularly in the past two decades.[2] One in six people is affected by allergic rhinitis.[3] In 1990 the estimated cost of hay fever in the United States was $1.8 billion.[4]

Effective medication for this condition is available, and prophylactic treatment (topical corticosteroids, sodium cromoglycate) should be started two to three weeks before the pollen season to prevent priming by allergen. This year the warm spring has advanced the pollen season by two to three weeks and treatment should be started earlier. After concern over the risk of cardiac arrhythmias, the Medicines Control Agency is currently converting terfenadine, a commonly used antihistamine that is available over the counter, into a prescription only drug.

Summary points

- The prevalence of seasonal allergic rhinitis is rising
- The peak months for seasonal allergic rhinitis are May, June, and July
- Later this year terfenadine, a popular antihistamine, will be converted from an over the counter to prescription only drug
- Pharmacotherapy controls symptoms for most people but should be started early

Methods

ost of the articles selected were from the personal library of GKS, who has 10 years of clinical and research experience in this subject. For an overview, we selected book chapters that had been written by leaders in the subject, while we selected individual papers for details of particular aspects of seasonal allergic rhinitis. Drug related details came from the *British National Formulary*, manufacturers' product data, and documents from the Medicines Control Agency.

Allergens

Seasonal allergic rhinitis is a type I immediate hypersensitivity reaction mediated by specific IgE antibody to a seasonal allergen, leading to mucosal inflammation characterised by sneezing, itching, rhinorrhoea, and nasal blockage. Pollens from wind pollinated grasses, trees, weeds, and spores from fungi are the commonest aeroallergens. Pollens are the male gametes of plants, and most antigenic pollens are 6-40 μm in diameter. Larger pollens from oil seed rape, which is pollinated by insects, have recently been implicated as causative agents.[5]

Timing

Grass pollen is the commonest cause of seasonal allergic rhinitis in Britain.[6] The highest levels of pollen in the atmosphere are found in May, June, and July. Flowering of plants occurs once every 4-12 days, mostly in the morning (4 am to 9 am). Pollen grains are carried high into the air around the middle of the day and fall in the evening as the air cools. Pollen concentrations of 50 grains/mm^3 are associated with symptoms in all susceptible people. Fungal spores are more prevalent from July to September. Warm, dry, and clear conditions increase levels of atmospheric pollen and spores. Increasing humidity and low nocturnal temperatures discourage pollination.

Recently, the role of "pauci-micronic" airborne particles carrying pollen allergen has been debated.[7] These particles may arise from plant material, leaves, and sap. Surface proteins of pollens may be transferred to small particles in the air through physical contact. Such interaction with air pollutants like diesel exhaust particles could increase the allergenic potential. Pauci-micronic particles are also formed in thunderstorms, when osmotic shock causes pollen grains to explode and release their constituent starch granules. These increase the atmospheric allergen load.

Epidemiology

A survey of 5349 adults in southwest London has shown the prevalence of seasonal symptoms to be 11%.[8] Seasonal allergic rhinitis has a peak prevalence in adolescence and early adulthood,[9] and there is no difference between the sexes in prevalence. Evidence of a rising prevalence comes from a study of Swedish

army conscripts, which found an increase from 4.4% of 55 393 conscripts in 1971 to 8.4% of 57 150 conscripts in 1981.[10] In Britain general practice consultations for hay fever have also risen,[11] and various other studies have indicated a similar trend.[12 13]

The prevalence is higher in the south than the north of Britain, possibly due to regional variation in the frequency of the atopic genotype or an exposure to aeroallergens in early life. The prevalence is higher among children from affluent households, and there is an inverse relation between the number of siblings in a family and the prevalence of hay fever.[14] Transmission of viral or bacterial infections from older children to their younger siblings in early childhood is thought to reduce allergic sensitisation. In vitro studies have shown that infections lead to a preferential stimulation of T1 lymphocytes over T2 lymphocytes, which play a vital role in the induction of an IgE response.[15]

Why is the prevalence increasing?

All atopic diseases are increasing.[9 16] In Japan a direct relation was found between sensitivity to pollen and proximity to areas with high levels of diesel exhaust particles in ambient air.[17] Animal studies suggest that these particles increase allergic sensitisation.[18]

Mechanics of allergy

On exposure to the allergen, antigenic proteins are dissolved in mucus and enter the nasal mucosa. They are engulfed by cells that present them to other immunocompetent cells (T and B lymphocytes), with subsequent production of specific antibody. In atopic people the local cytokines (interleukin 4, interleukin 13), and T2 lymphocytes encourage an IgE response. The Fc portion of this IgE antibody binds to high affinity receptors on the surface of mast cells.

Future exposure to the allergen causes a cross linking of two or more IgE molecules and degranulation of mast cells. This leads to release of biochemical mediators which act on local cells, nerve endings, and vasculature.[19-22] This is the early phase reaction. Recruitment of inflammatory cells continues after this phase, and the nasal lining is unduly sensitive to allergen exposure and non-specific stimuli. This is called priming. In this state a much reduced dose of allergen can elicit a full response. About 30-40% of patients experience a resurgence in their symptoms about 6-12 hours after initial exposure. This is the late phase reaction. In hay fever these three responses can occur simultaneously in different parts of the nasal mucosa.

Mediators and cells

Nasal allergen studies have enhanced our understanding of the pathophysiology of hay fever.[23] Increased levels of proinflammatory mediators like histamine, tryptase, prostaglandin D_2, and leukotrienes are seen in nasal lavage fluid after an allergen challenge. These mediators are derived from mast cells in the early phase. Plasma exudation is also a major feature in early phase reaction. This provides kinins, which play a role in pathogenesis. Eosinophil cationic protein, cytokines, and major basic protein are the predominant mediators in the late phase. Eosinophils seem to be responsible for ongoing inflammation.

Clinical features

The cardinal symptoms of seasonal allergic rhinitis are sneezing, rhinorrhoea, itching, and nasal obstruction. Nasal discharge is clear and watery. Pruritus affects the nose, eyes, and palate. Nasal obstruction is more pronounced in the late phase reaction. Pollen contact with eyes causes soreness, and sensitive subjects show congestion and periorbital oedema. Some 13-38% of patients also have asthma,[9] and eczema is also more common. This implies a genetic basis for this disease. Patients are more likely to have the same disease manifestation of their atopy as their parents.[24]

Diagnosis is made on a good clinical history and confirmed by skin prick testing with the subcutaneous method, which is cheap, rapid, and safe. Negative and positive controls are essential to interpret the results correctly. Patients who have recently taken antihistamines are likely to give false negative results. In patients with dermographism, severe dermatitis, or a history of anaphylactic reaction these tests are contraindicated, and a radioallergosorbent blood test is used instead. This is expensive, less sensitive than a skin test, and is more quantitative. Serum levels of IgE antibodies correlate well with the severity of symptoms. Over a three year period there is an 8% spontaneous cure rate for hay fever.[6] This is related to a gradual decrease in specific IgE levels.

Management

Patient education

Most patients treat themselves with over the counter drugs. To avoid misuse of such drugs, the British Society of Allergy and Clinical Immunology has devised guidelines that are displayed at pharmacy counters.

Allergen avoidance—Hay fever sufferers can take basic measures to avoid exposure to allergens.

- Listen to pollen forecast and plan day accordingly (telephone 01705 77 77 220 for pollen count)
- Avoid cutting grass, picnics, camping
- If out in countryside, shower and wash hair on return
- Wear wrap around sunglasses when outside
- Before evening (when pollen descends as air cools)
  Bring in washing
  Close bedroom windows
- Keep car windows closed, and consider buying an air filter for the car
- Avoid smoking and other irritants such as fresh paint
- Avoid other allergens that affect you.

Drugs

Table 1 summarises the effects of different drugs on symptoms of seasonal allergic rhinitis.

Table 1 Effects of drug treatments on symptoms of seasonal allergic rhinitis

	Nasal itching and sneezing	Rhinorrhoea	Nasal obstruction	Impaired smell
Sodium cromoglycate	+	+	+/–	–
Topical decongestants	–	–	+++	–
Oral antihistamines	+++	++	+/–	–
Ipratropium bromide	–	+++	–	–
Topical corticosteroids	+++	+++	++	+
Oral corticosteroids	+++	+++	+++	++

Drug treatment of seasonal allergic rhinitis in children

Prophylaxis
- Sodium cromoglycate *or*
- One of the following
  Fluticasone propionate (ages >4 years)
  Beclomethasone (ages >6 years)
  Flunisolide (ages >5 years)
  Triamcinolone acetonide (ages >6 years)

Relief
- Antihistamines (local)
  Azelastine (ages >9 years)
- Antihistamines (oral)
  Cetirizine (sugar-free syrup)—5 mg daily (ages 2-6 years), 10 mg daily (ages >6 years)
  Loratadine—5 mg daily (body weight <30 kg, ages 2-12 years), 10 mg daily (body weight >30 kg)
  Terfenadine (sugar-free syrup)*—15 mg twice daily (ages 3-6 years), 30 mg twice daily (ages 6-12 years)
  Astemizole*—5 mg daily (ages 6-12 years)
- Sedating antihistamines impair academic performance[25] and should be avoided

*See special precautions that apply to these drugs

Decongestants

These are available over the counter as drops and tablets. They relieve nasal obstruction but may increase rhinorrhoea. Patients with marked nasal obstruction may benefit from taking topical decongestants for a maximum of five days. Continuous use can lead to rhinitis medicamentosa, a condition characterised by excessive rebound nasal congestion. Imidazoles (such as xylometazoline), are more likely to cause this, because of their longer duration of action.[26] Oral decongestants are not particularly effective and cause insomnia and hyperactivity.

Sodium cromoglycate

This is available as a nasal spray or as eye drops. It stabilises cell membranes and prevents the release of mediators, and probably also inhibits chloride channels and is a tachykinin antagonist.[27] It prevents both the early and late phase responses. Full therapeutic effect is seen after two weeks of regular use (two sprays in each nostril four times daily, falling to one spray four times daily after 10 days). It is most effective if started early and used regularly prophylactically. Its efficacy is less than that of topical corticosteroids and similar to that of antihistamines. Ophthalmic preparations are available for patients with eye symptoms (one or two drops in each eye four times daily).

Safety precautions with terfenadine and astemizole

- Do not exceed recommended dose
- Avoid use in patients with
  Cardiac disease
  Hepatic disease
- Do not use concurrently with:
  Ketoconazole, itraconazole, or related imidazole antifungal drugs
  Erythromycin, clarithromycin, or related macrolide antibiotics
  Neuroleptics
  Tricyclic antidepressants
  Diuretics
  Astemizole (terfenadine)
- Do not take with grapefruit juice

Antihistamines

Antihistamines are competitive antagonists of histamine for H_1 receptors. Some second generation antihistamines have weak anti-inflammatory effects.[28] Older generation antihistamines cause drowsiness and compromise motor skills in 10-25% of patients.[29] New antihistamine molecules are lipophobic and do not cross the blood-brain barrier, thus preventing this adverse effect. The dose for astemizole, loratadine, and cetirizine is 10 mg once daily; for terfenadine it is 60 mg twice daily; and for acrivastine, which has a short half life, it is 8 mg three times daily.

Terfenadine and astemizole have a quinidine-like action at increased blood concentrations and can prolong the QTc interval, precipitating ventricular tachyarrhythmias. They are contraindicated for patients with hepatic impairment or cardiac disease and should not be used by patients taking macrolide antibiotics or antifungal drugs since these can compete for hepatic metabolism and increase blood concentrations (see box). Terfenadine has been banned by the Food and Drug Administration, but the Medicines Control Agency noted its extensive use (six billion patient days since its introduction in 1981) and its safety profile in recommended doses, and, instead, it will revert to a prescription only medicine.

Cetirizine, which is excreted unchanged in the urine, is the safest choice in such patients. Loratadine, which is partially hepatically metabolised, has no quinidine-like activity at raised blood concentrations. Like cetirizine, it has a low incidence of cardiac events but with fewer reports of sedation. Fexofenadine, the active metabolite of terfenadine, is non-sedating and has no effect on the QTc interval, and it has recently been launched in Britain. Sedation by first generation antihistamines is probably a greater cause of morbidity and mortality than the cardiac effects of second generation drugs.

Azelastine and levocabastine are H_1 receptor antagonists available in topical form as nasal spray and eye drops. Well controlled comparative clinical trials with oral antihistamines have shown levocabastine to be as effective as oral preparations in providing symptomatic relief. There is minimal systemic absorption, which is not clinically important, and so this drug may prove beneficial in pregnant and lactating mothers.[30]

Topical corticosteroids

These drugs prevent the synthesis and release of mediators and inhibit the migration of inflammatory cells to the nose. Treatment is best started prophylactically about two weeks before the pollen season and continued regularly throughout the season.

For rapid relief, betamethasone nose drops are useful (two drops in each nostril twice daily, with the head down and forward). Once symptoms are controlled, the nose drops can be substituted by a spray such as beclomethasone dipropionate or fluticasone propionate (two puffs in each nostril once or twice daily (that is, 200-400 µg/day)). Two recent additions are mometasone furoate, which has an excellent safety profile, and triamcinolone acetonide, which is less

likely to run out of the nose or down the throat. Comparative studies have shown that topical corticosteroids control symptoms more efficiently than antihistamines and reduce the number of days off work.[31] Topical corticosteroids and antihistamines can be combined in patients with more severe problems.

Nasal burning and irritation are seen in a few patients. This may be due to benzalkonium chloride, which is used as a preservative in all nasal sprays except budesonide. Systemic absorption and adrenal suppression are not seen unless the daily intake exceeds 800 μg in children and 1200-1500 μg in adults.[32]

Systemic corticosteroids

Intramuscular depot preparations such as triamcinolone (Kenalog) are popular with patients, but the dose obviously cannot be reversed should side effects occur. The maximum dose is also given at the start of treatment whereas rising allergen concentrations later in the season prime the nose and result in increased sensitivity at a time when the drug effect is waning. Local muscle wasting also occurs with repeated use. For patients with severe symptoms despite treatment with topical corticosteroids and antihistamines, a better alternative is the occasional, intermittent use of oral prednisolone (0.1-0.2 mg/kg) in the morning on days when the pollen count is high or some special event such as exams or a wedding is taking place.

Antileukotrienes

These fall into two groups—leukotriene receptor antagonists and inhibitors of leukotriene synthesis. Both are oral drugs and effective against rhinitis in clinical trials, with an efficacy similar to that of antihistamines. Some representatives of this drug category will shortly be available in Britain. Their place in the treatment of hay fever remains to be determined.

Immunotherapy

Immunotherapy involves the administration of standardised extracts from pollen allergen with the aim of reducing target organ reactivity and cell sensitivity.[33] The clinical efficacy of this treatment has been proved by well controlled trials,[34 35] but all aspects of management are open to debate. Selection of patients is critical, and guidelines exist for specific indications.[36 37] Treatment should be done by experienced specialists and in departments with full resuscitative facilities because of the danger of anaphylaxis.

Immunotherapy is indicated in patients with severe rhinoconjunctivitis whose symptoms have failed to resolve with conventional treatment.[38] The treatment is contraindicated in patients with severe seasonal asthma, immunodeficiency syndromes, malignancies, and psychological disorders.

The preferred route of administration is subcutaneous. The lack of consensus on most aspects of immunotherapy and the risk of severe systemic reactions have limited its popularity. However, peptide immunotherapy, which is directed against T cells, is theoretically safer since anaphylaxis should not occur.

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