Update

New developments in the field of allergy and asthma

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Asthma prevalence and immunogenetics

Asthma has increased in nearly every part of the world studied,[1] even in populations where the gene pool has not altered much in recent years.

The interplay between the genes and environment is an intriguing one. Migration studies[2] have shown that asthma prevalence and bronchial hyperreactivity increase as a Western lifestyle is adopted. This has not only been shown in Africa, but also in other parts of the world, e.g. China (Hong Kong), South America and the Middle East.[1]

In developed countries such as the USA it has been observed that certain ethnic groups who now reside there have higher prevalences and more severe asthma than other ethnic groups. This is illustrated by higher prevalences and more severe asthma in American Puerto Ricans than in those of Mexican origin. Such differences have suggested that there may be susceptibility genes which facilitate the development of asthma in a certain environment. Conversely, other genes may protect against the development of asthma.

Genes which may have been believed to influence the development of asthma include the beta-2 receptor gene, genes for the expression of the glucocorticoid-binding receptor and those responsible for the expression of allergy.

Recently Professor Eugene Bleeker discussed the current status of candidate genes for asthma in the World Allergy Organisation's 'Conversations in Allergy' on line, at the American Academy of Asthma, Allergy and Immunology (AAAAI) Congress in Philadelphia, March 2008.

Beta-2 receptor gene

Beta-2 receptor gene polymorphisms are believed to influence not only asthma severity, but also response to beta-2 short-acting and long-acting agonists. There are now 27 variations of the human beta-2 receptor gene.

Regarding the Arg/Gly polymorphism, 12 - 14% of American Caucasians are homozygous and 22 - 24% of African Americans are homozygous.

Individuals who have the Arg/Arg haplotype behave differently compared with those who have the Arg/Gly haplotype, when they receive intermittent versus regular short-acting beta-2 agonists. It has been of interest to note that the Puerto Ricans in the USA generally have been receiving frequent treatment with short-acting beta-2 agonists. For the long-acting beta-2 agonists however, detrimental effects have not been shown to be related to the presence of an Arg/Arg polymorphism of the beta-2 adrenergic receptor in studies

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of both formoterol and Serevent, used in combination with a steroid.

Other asthma susceptibility genes

There are a number of genes being studied because they influence the expression of proteins, molecules and cytokines, which are important in the immunopathology of asthma and allergies.

Important susceptibility genes include the IL4 receptor alpha gene, IL4 gene, the IL13 gene, Stat 6 genes regulating IgE expression, Adam 33 and the HLA-G genes.

Variations in the IL4 receptor gene have correlated functionally with a population of severe asthmatics who have required ICU admission, mechanical ventilation and persistent eosinophilia.

Current studies in progress by Professor Donetta Vercelli (Arizona), also highlighted at the AAAAI meeting in March 2008, indicate that variations in the promoter for the IL13 gene influence transcription in B cells and may influence transcription of IgE by up to 50%.

Although TNFα is believed to play an important role in severe asthma, therapeutic studies with anti-TNFα have been disappointing. In spite of this, rare genotypes for TNFα have been associated with more severe exacerbations and may represent a genetic marker for severity.

Studies looking at the efforts of combinations of different genes in asthma are on the horizon. Clustering of certain genotype polymorphisms may well identify the asthmatic who is likely to be more severe and require intensive treatment and surveillance. In addition gene mapping may also guide the clinician as to which anti-asthma medications may be more effective, or should be avoided in view of possible side-effects.

With the availability of gene microchips and microarray technology it may be cost effective and worthwhile to identify and

profile a host of asthma genes in a particular severe asthmatic using computerised technology, to guide the clinician to the most appropriate treatment for a given patient, bearing in mind the wide heterogeneity of the asthmatic phenotypes in the population.

Reasons for the increase in asthma and allergy prevalence

In addition to genetic factors, environmental factors play a critical role in the expression of allergic diseases. Examples of external factors which influence the expression of asthma and allergies are lack of exercise, obesity, changes in diet, Western lifestyle, time of exposure to allergen, context of exposure to allergens, breast-feeding, the indoor environment and reduction in childhood infections as a result of immunisation.

Many of these environmental-host effects are explained by the important immunological processes which take place in the first 2 years of life, which normally protect one from developing allergies.

Pregnancy is a state of T helper-2 (Th-2) dominance which protects the mother from rejecting the fetus immunologically. After birth, the effects of exposure to endotoxin and similar molecules physiologically drive the immune response to that of a modified Th-2 response, with the production of important cytokines such as interleukin-10 and TGF-beta, and the activation of $CD25^{+}$ regulatory T cells which dampen down the TH-2 response and its allergy-inducing cytokines (IL-4, IL-5, IL-3). This results in the reduction in IgE levels, eosinophil and mast cell activation. When stimulated with strong stimuli for the switch to a TH-1 (gamma interferon) immune response, e.g. BCG or tuberculosis, a TH-1 immune response predominates, providing protective immunity reducing the likelihood of expressing allergic disease.

Allergy diagnosis

The history remains the cornerstone of making an accurate allergy diagnosis. This should include a detailed family history, a history of food and skin allergies (e.g. eczema) in infancy (particularly with sensitivity to egg and milk) and a careful history of exposure of allergen in relation to symptoms. This applies to seasonality of symptoms for inhalant allergens. The temporal relationship between exposure and symptoms in the case of food allergies is critical in diagnosing a type 1 allergic response.

Serum tryptase determination is an excellent confirmation of an anaphylactic reaction during anaesthesia. Tryptase levels are also significantly elevated in systemic mastocytosis.

Total IgE levels, when elevated, generally correlate with the presence of allergic disease, particularly in the case of eczema, but may be normal in subjects with allergic rhinitis, asthma and food, or drug allergy.

Total IgE levels were previously found to be higher in South African non-Caucasian patients, possibly related to parasite infestation. A recent study by Levin *et al.*[3] in Xhosa adolescents showed no significant difference when compared with Caucasian counterparts in the Cape Town area.

Skin prick testing or Immunocap RAST tests using a panel of 8 - 10 common inhalant allergens is a very effective screen for allergy in patients with allergic rhinitis or asthma. Such a panel should include house dust mites (Der p 1 and Der f 1), and Bermuda grass, Rye grass, cockroach, cat, dog, alternaria, *Cladosporium*, *Aspergillus* and *Epicoccium*. Tree pollens cause allergic symptoms usually earlier in spring (e.g. oak, plane) whereas others may be important after spring (e.g. cypress). Tree pollens are also important in the Gauteng area. Foods are an unusual cause of allergic rhinitis and asthma.

An increasing number of adults complain of intolerance to wheat products, mostly processed wheat.

Food allergy

There have been significant advances in the understanding of the proteins and the diagnosis of food allergy in the past few years, in children and in adults. It is important for the clinician to appreciate that more than 70% of adverse reactions to foods perceived by patients are not true allergies, but food intolerance, or toxic reactions. Food intolerance is usually suggested by the reaction occurring an hour or more after exposure to the food, a dose response, or inconsistent effect, or a reaction to a food that has been processed.

Some of these reactions are due to preservatives such as sulphur dioxide, sodium benzoate, sodium nitrate and colourants, and sensitivity can be confirmed using the Cellular Activated Sulphido Leukotriene Release Test (CAST) on fresh blood samples.

True food allergies are confirmed by skin prick tests, Immunocap RAST tests and by food challenge, depending on the results of the skin or laboratory tests. In infancy common food allergies include egg, milk, peanut, fish, soya and wheat. Most of these disappear by the time the child goes to school. In the case of peanuts, about 20% will have persistent and severe sensitivity to peanut throughout their lives.

Food allergies which usually appear during or after adolescence include seafood allergies and fruit allergies responsible for the oral allergy syndrome. This syndrome, more common in women, involves a rapid swelling of the mouth, lips and face with some abdominal cramps and rarely causes asthma or rhinitis symptoms, but may result in anaphylaxis in some cases. Foods important in the oral allergy syndrome include the summer fruits melons, kiwi, peach, mango, bananas and plums.

Some of these are unstable allergens which cannot be confirmed by Immunocap RASTs, but may be confirmed with skin testing using freshly prepared extracts from the fresh ripe fruits.

There appears to be a wide variation in the sensitivity to different species within a fruit (e.g. apple) and most of the proteins are in the skins of the fruits. Many of these patients can eat peeled cooked (stewed) fruit or jam, but not the fresh ripe fruit. In the case of nut allergies 50% of the patients who react to peanuts (actually a legume) also react to tree nuts (e.g. Brazil nut, hazel nuts, pine nuts, macadamia, sesame).

Allergens to tree nuts and seafood are usually severe allergies and may be life threatening. An increasing number of adults complain of intolerance to wheat products, mostly processed wheat.

These reactions are typically delayed, involve the gastro-intestinal tract and patients complain of a range of nonspecific symptoms including bloating, dyspepsia and tiredness. The diagnosis is best confirmed by elimination and challenge of wheat-containing foods and the CAST or ImmunoCAP test or skin test is always negative in such cases.

Some patients with food allergy react to cross-reacting allergens in the fruits, including lipid transfer proteins and chitinases and in the case of kiwi and avocado and banana, may also be allergic to latex. This is more common in health care workers and people exposed to latex-powdered gloves on a regular basis.

New tests for food allergy include micro-array chip technology which will

detect hundreds of different specific IgE responses to a particular food using less than a millilitre of serum. In the case of seafood allergens the tropomycins are common IgE-reacting determinants present in molluscs and crustaceans, but also in house dust mites and can explain clinical cross-reactivity.

Drug allergy

Drug allergy remains one of the most challenging areas in the field of allergology. This is partly related to the number of new drugs emerging on the market each year, but also to routes of administration, the presence of allergenic excipients in drugs and the misuse of prophylactic antibiotics and cocktails of drugs prior to surgical procedures.

Allergy to the penicillins and cephalosporins remains the most common of antibiotic allergies.

Recently an increase in reporting of ceftriaxone hypersensitivity has been observed in the Allergy Diagnostic and Clinical Research Unit of the University of Cape Town, some with life-threatening anaphylaxis. Allergy to penicillins and cephalosporins may be to the common beta-lactam moiety, but some penicillins and cephalosporins also share side-chains on their molecules, which can be allergenic and also account for cross-reactivity. The fourth-generation cephalosporins are less likely to cross-react with penicillin than the older cephalosporins which shared side-chains with some of the penicillins.

Non-steroidal anti-inflammatory drug hypersensitivity is also emerging as a common and serious clinical allergy.

Life-threatening allergic reactions may occur to ibuprofen, indomethacin, aspirin, diclofenac, fenoprofen, naproxen, sulindac, celecoxib and acetaminophen.

Fixed drug reactions have been reported for indomethacin, aspirin, mefenamic acid, diclofenac, piroxicam and paracetamol. Non-steroidal anti-inflammatory drugs may also cause photo contact dermatitis (e.g. diclofenac, ibuprofen, flufenamic acid).

Risk factors for adverse reactions to drugs include diseases such as AIDS and conditions with recurrent infections (e.g. cystic fibrosis), where multiple antibiotics are required because of the development of resistance to antibiotics.

Type 1 allergy to sulphonamides is the second most common antibiotic allergy and was commonly a problem in patients with AIDS, being treated prophylactically for *Pneumocystis carinii* chest infections.

Recently with the advent of HAART (highly active antiretroviral treatment) the number of these patients requiring sulphonamides has reduced. A delayed febrile reaction 1 - 2 weeks after commencement of therapy, accompanied by a morbilliform rash, is also observed in the HIV setting and is thought to be an immune complex (type 3 Gell and Coombs) reaction. Stevens-Johnson syndromes are also an important serious side-effect of sulphonamide therapy.

Angioedema due to ACE inhibitors is another new and common presentation in the allergy clinic. It usually involves the mouth, tongue, lip and upper airway and can cause life-threatening angioedema. The onset may occur weeks or years after the patient has started ACE inhibitor therapy and subsides completely on withdrawal of ACE inhibitors. There are no laboratory tests for ACE inhibitor allergy.

Testing for drug allergy is very limited. For penicillin and cephalosporin allergy, a combination of RASTs, skin prick testing and challenge in a special unit is most reliable. For other drugs, skin testing and laboratory tests are too insensitive to guide the doctor and confirm sensitivity. When a drug is essential, and clinically indicated, desensitisation may need to be conducted in an ICU setting. Protocols are available for the penicillins, cephalosporins and sulphonamides.

The need for these procedures is best assessed by allergologists and they should be performed by physicians experienced in resuscitation.[4,5]

Rhinitis guidelines

The ARIA guidelines were updated in 2006[6] and include new information sourced from publications up to the end of 2004. The updated report has emphasised the safety of the new-generation non-sedating long-acting antihistamines. The ARIA guidelines encourage a phased approach to the treatment of allergic rhinitis, commencing with antihistamines in those in whom the disease is short lived, with rhinorrhoea, sneezing and itching as predominant symptoms, but to also use intranasal steroids in those who are more severe, even if the disease is short lived.

Antihistamines are still preferred for primary care of more mild disease, especially since nearly all of the new-generation antihistamines have been found to have anti-inflammatory activity, in addition to their antihistamine effects. A role for olopatadine in chronic allergic rhinitis and possibly for anti-IgE monoclonal antibody is also addressed in the guidelines. The guidelines stress that allergen immunotherapy is the only treatment which will change the natural history of allergic disease. The use of the older sedating antihistamines is strongly discouraged for the treatment of allergic rhinitis. Unfortunately they are still abused by patients who obtain them easily as over-the-counter medicines. Leukotriene receptor antagonists (e.g. montelukast) are optional treatments to antihistamines for rhinitis, especially in asthmatics.

Asthma guidelines

Global guidelines for asthma have been updated[7] and adapted for South African adults and adolescents.[8] Treatment guidelines are provided depending on the 'level of control' of asthma, rather than a 'severity grading'.

Details of the algorithms for treatment are readily accessible on the website,[7] which provides a comprehensive new approach to the assessment of adult asthmatics. Important messages in the new guidelines include a warning that long-acting beta-2 agonists should never be prescribed as single therapy without inhaled corticosteroids. Leukotriene receptor antagonists (e.g. montelukast) are recommended for all levels of severity and control as 'add-on' to inhaled steroids, but may be tried as an alternative as monotherapy in milder asthmatics, especially with exercise-induced asthma.

Immunotherapy is a highly cost-effective option when compared with lifelong antihistamines, inhaled or intranasal steroids, asthma and rhinitis morbidity and hospitalisations for asthma.

There is heterogeneity in response to leukotriene receptor antagonists (LTRAs) among asthmatics. Responders do not develop tolerance and in view of their beneficial effect on rhinitis symptoms, LTRAs are particularly indicated in those patients who have both asthma and rhinitis. In children leukotriene antagonists may be used as monotherapy in those with milder

symptoms and are especially effective in exercise-induced asthma. Add-on therapy with anti-IgE monoclonal antibody is reserved for those with elevated IgE levels who have severe uncontrolled asthma, and inhaled steroids are now preferred to the older treatments (e.g. theophyllines, cromoglycates). Combination therapy with LABAs has a steroid-sparing effect.

Although the new guidelines emphasise treatment in relation to 'level of control', it is important that the level of intensity of treatment of an individual patient should be modified if they have certain risk factors for relapse. For children, these include a recent hospitalisation, multiple allergies, fungal allergies, peanut allergies, inner-city children, children in a crèche and those who have inadequate caregivers or those in whom excessive beta-2 agonists have been used to obtain 'control'.

Useful new guidelines have recently been published in Europe (PRACTALL 2008)[9] for treatment of children under 5 years.

Immunotherapy

Based on evidence provided in Cochrane Reviews, meta-analysis and double-blind placebo-controlled studies, both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy can be recommended as curative treatment for subjects who are predominantly monosensitive to grass pollen and house dust mites, for rhinitis and for mild to moderate asthma.[10,11] Immunotherapy is also the treatment of choice for patients with life-threatening (grade III and IV) bee and wasp venom hypersensitivity.

In practice, sublingual immunotherapy (SLIT) has become a more convenient, very practical and effective treatment for allergic patients, since it is extremely safe and can be conducted at home.

Follow-up studies with asthmatic test subjects conducted over a period of 10 years have confirmed the long-term effectiveness of SLIT.[10] Although this therapy is not yet registered in South Africa and more convenient formulations (e.g. dissolving sublingual tablets) are being developed, SLIT and SCIT may be prescribed on a named-patient basis with permission from the Medicines Control Council.

Immunotherapy is a highly cost-effective option[11] when compared with lifelong antihistamines, inhaled or intranasal steroids, asthma and rhinitis morbidity and hospitalisations for asthma. Their selected use is therefore encouraged, and guidelines and patient information brochures as to their use and availability are available through the Allergy Society of South Africa.

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Single Suture

Treatment for progeria?

Two common drugs have reversed the effects of progeria in mice – and they have few side-effects, so may one day be used in children with the disease. Progeria accelerates from early childhood and is usually fatal before puberty. There is currently no cure. The disease is caused by gene mutations that disrupt production of the protein prelamin A, found inside the nuclei of cells. The damaged prelamin A binds to molecular fragments in the body called farnesyls, which then bind to the nuclear membrane, causing the build-up of protein that underlies the disease.

Statins and bisphosphonates are known to reduce farnesyl levels. This led Carlos López-Otín to speculate that they may be able to reverse progeria. The team gave a mixture of the two drugs to progerid mice and found that this reduced ageing symptoms and the mice lived longer than controls. Researchers are now seeking permission for research on humans.

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