Samter's triad

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Children with asthma often have specific allergies. For those patients whose asthma begins as an adult, the cause is often not a true allergy. One such example of this is Samterôs Triad. This is a condition in which patients have a combination of symptoms such as airway problems like asthma; nasal problems like blockage and running discharge with nasal polyps; and then develop a hypersensitivity reaction to aspirin. This hypersensitivity reaction is non-allergic.

Where it all began

This condition was first described in 1922 by Widal et al. The article was published in French, and largely ignored for the next 45 years. It wasnôt until 1968 when Samter and Beers described patients with the symptom triad of asthma, aspirin sensitivity and nasal polyps that the condition became recognised and known as Samterôs triad. Chronic hyperplastic sinusitis (enlargement caused by excessive multiplication of cells) is now considered a fourth hallmark of the disease, with the preferred name now being aspirin exacerbated respiratory disease (AERD).

The symptoms

The nasal symptoms are not just nasal polyps but can include rhinitis (inflammation of the nose) with sneezing, running of the nose, and congestion. Anosmia (loss of smell) is also typical. In fact in one study, a normal sense of smell correlates strongly with not having AERD. The asthma consists of the usual symptoms such as wheezing, cough and chest tightness. Facial flushing may also occur. Patients typically develop rhinitis within their early thirties, which may not respond to the usual medications. It is often later on that loss of smell, nasal blockage, sinusitis, and then finally asthma intervene. The aspirin sensitivity may also only become clear with time.

AERD can often appear in people who already have true allergic rhinitis or asthma. In one study of 300 AERD patients, 64 per cent had positive skin prick tests to environmental allergens and most had clinical allergic respiratory tract disease. This also means that in one thirdof the patients, AERD appeared without any previous associated allergic disease.

What is the underlying cause of Samter’s triad?

So why isn't this a true allergy? Samter's triad is sometimes referred to as a pseudo-allergy. True allergy is triggered by immunoglobulin E (IgE), an antibody which reacts to some foreign substances in sensitive individuals. Samter's triad is a pseudo-allergy because it produces allergy-like symptoms but through a different mechanism. Aspirin and non-steroidal anti-inflammatories (NSAIDs) block an enzyme called cyclo-oxygenase1 (COX1); this is thought to lead to an excess of substances called leukotrienes, which produce the severe allergy-like effects.

What is aspirin sensitivity?

Aspirin sensitivity refers to deterioration in symptoms 30 minutes to three hours after aspirin ingestion. Patients often react to other anti-inflammatories such as Brufen (nurofen) or Voltaren (Diclofenac), also known as NSAIDs. These can also be present in cough or cold preparations, such as lozenges, so patients need to read the labels of these. The reaction seems to be a dose-related effect, with small doses causing mild symptoms and larger doses eliciting more severe reactions. The reaction is also a class effect so the chance of cross-reaction from one NSAID to another, providing they are given at full therapeutic doses, is close to 100 per cent.

So how common is it?

Amongst asthmatics, a meta-analysis of studies has estimated the prevalence at 21 per cent. In those that have significant nasal symptoms or abnormal sinus CT scans as well as asthma, the prevalence was even higher at 30 per cent to 40 per cent.

So how is AERD diagnosed?

The diagnosis is made with a clinical history and sometimes an aspirin challenge. If aspirin/NSAID sensitivity is obvious from the patient's history an aspirin challenge may not be necessary. For those in whom aspirin sensitivity is suspected but not definite, an aspirin challenge is the only definitive method of diagnosis. Without aspirin sensitivity demonstrated, the diagnosis cannot be made.

In one study of 300 patients, CT or plain radiographs of the sinuses showed them to be completely opaque in 96 per cent of cases, with thickening of the mucoperiosteum (mucous membrane and dense covering of bone united to form a nearly single membrane) in 6 per cent. Therefore a patient with normal smell and normal CT sinuses does not have AERD.

The aspirin challenge test should be performed by an allergy or respiratory specialist with necessary medications, equipment and support staff, because reactions can be significant. If the

patient has a history of a very severe reaction, such as anaphylaxis, the test may need to be performed in an ICU. Antihistamines may be withheld prior to the test and patients may be pre-treated with a leukotriene-modifying agent such as Singulair. This has been shown to decrease the severity of respiratory reactions, but not alter nasal reactions so the test result is still usually clear. If the patient is taking oral and topical corticosteroids, or long-acting bronchodilators, these should be continued but antihistamines may be stopped.

Do all patients need an aspirin challenge?

One study found that in patients with a history of reactions to NSAIDs, the chance of a positive aspirin challenge was 86 per cent (198/231). If the patient had experienced two reactions this rose to 89 per cent. If the patient had been admitted to ICU the test was positive in 100 per cent (45/45). Therefore patients with good histories of significant clear NSAID reactions do not need an aspirin challenge. It also shows just how dangerous full doses of NSAIDs can be to patients with AERD. Alternatively, those with no history of aspirin sensitivity require a challenge for this diagnosis and the yield can be significant, with only 3 per cent of asthmatics reporting a history of reacting to aspirin or NSAIDs, when tested the positivity was 21 per cent. For patients with nasal polyps and pan-sinusitis, this increased to 42 per cent in one study of 12 patients.

How is AERD treated?

First and foremost, NSAIDs and aspirin, in all their forms, should be avoided. Controlling the symptoms with medical therapy needs to be attempted in the first instance. For some with mild disease Singulair may control their symptoms; however many end up on multiple medications. In one study of 300 patients referred for aspirin desensitisation, one third was on daily corticosteroids, with a further 45 per cent requiring short courses.

If medical therapy fails, as can often happen, the patient should be referred to an otolaryngologist for consideration of surgery. AERD patients tend to have a large amount of polypoid tissue (ie polyps) and there is significant re-growth, with the average re-operation time for nasal polyps of just three years.

Aspirin desensitisation is a process where patients gradually take progressive amounts of aspirin starting from a dose of just 10mg. The aim is often a dose of 325mg but can be up to 650mg twice daily. Multiple studies have demonstrated the efficacy of aspirin desensitisation.

Patients have improved asthma symptoms; improved nasal symptoms; fewer sinus infections; fewer requirements for nasal, inhaled and systemic corticosteroids; fewer hospitalisations for asthma; and less sinus surgery. One study found the average

time before a patient required further sinus surgery increased from an average of three to 10 years. Improvements in symptoms have been statistically significant within one month.

The problem over time can be discontinuation of aspirin. If this is for 24 or 48 hours only, the aspirin can be re-started at the same dose. If it was stopped for three days, the aspirin cannot be re-started until the desensitisation process is done from the start again. Also, at higher doses some patients get side-effects like indigestion. This has caused people to stop their aspirin therapy in 14 -40 per cent of patients at one year. For this reason the dose is sometimes 325mg or less, but the effectiveness of this is unclear.

Which AERD patients should be referred for aspirin densensitisation? If a patientôs symptoms are mild, avoiding NSAIDs and aspirin may be all that is necessary. However, if the symptoms are problematic despite optimal medical therapy, corticosteroids are regularly required,. If the patient is requiring nasal or sinus surgery, or needs aspirin or NSAIDs for another medical reason, then he/she should be referred for aspirin desensitisation.

The question arises, what can a patient with AERD now take for pain relief? Paracetamol is a weak COX1 (an enzyme) inhibitor so at high doses may induce a mild reaction. The same is true for partially selective COX2 inhibitors such as Meloxicam. Given that patients with AERD cannot use NSAIDs, they are sometimes prescribed a different type of anti-inflammatory for pain called a COX2 inhibitor. In one study of 172 patients with AERD, none reacted to a COX2 inhibitor.

There have been isolated case reports of clear reactions; however this seems to be rare, on current evidence, albeit relatively limited. Despite this, warning labels on all coxibs list AERD as a contraindication for prescribing COX2 inhibitors, which most allergists would consider more as a caution. The possibility exists that these case reports are due to a different mechanism such as IgE mediated. Standard of care is for the first dose of a COX2 inhibitor to a patient with AERD to be given in a physicianôs office.

Should patients with asthma but no known AERD have their first ever dose of an NSAID as a test dose in a physician's office?

The major risk of death comes when a full therapeutic dose of NSAID is given to an asthmatic patient in middle age. However, 80 per cent of asthmatics actually tolerate these often useful medications without reaction. When practical, the first dose of an NSAID in an asthmatic patient should be given in a physicianôs office. This is absolutely essential if a patient has anosmia, sinusitis or nasal polyps, when the chances of reaction may be 40 per cent.