

# Rhinosinusitis and nasal polyposis in aspirin sensitive and aspirin tolerant patients: are they different?

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Hypersensitivity to aspirin (acetylsalicylic acid; ASA) is present in 5–10% of asthmatic patients and is associated with chronic rhinosinusitis and nasal polyposis, a syndrome referred to as the aspirin triad.<sup>1,2</sup> The mechanism of the hypersensitivity reaction to aspirin is not immunological, but may be related to the inhibition of cyclo-oxygenase, an enzyme responsible for prostaglandin synthesis, by aspirin.<sup>2</sup> A positive history of aspirin hypersensitivity, which is the hallmark of this syndrome, is a significant and reliable indicator of chronic intractable rhinosinusitis, persistent asthma of greater than average severity, and higher than ordinary medication requirements, including dependence on steroids.<sup>1,3</sup> In addition to bronchospasm, most aspirin sensitive asthmatic subjects challenged with aspirin develop nasal symptoms including rhinorrhoea, sneezing and nasal obstruction, but the nasal responses to aspirin are superimposed on the existing pathology of the upper respiratory tract. The incidence of sinusitis identified by radiography in aspirin sensitive asthmatics may be up to 96.2% and the frequency of nasal polyps may be as high as 70.8%<sup>2,4</sup> compared with 6.7% in the general asthmatic population.<sup>5</sup> A subgroup of aspirin sensitive patients has a reaction exclusively in the upper respiratory tract. They do not have asthma but the clinical picture of nasal disease (hypertrophic rhinosinusitis) in these patients is similar to that observed in patients with the aspirin triad.<sup>6</sup>

This article reviews the similarities and differences in the severity, pathophysiology, and management of upper airway disease in aspirin sensitive and aspirin tolerant patients with asthma and chronic rhinosinusitis.

## Is the rhinosinusitis more severe in aspirin sensitive patients?

It is generally assumed that chronic rhinosinusitis in aspirin sensitive asthmatic patients is more severe than in aspirin tolerant patients. A high recurrence of nasal polyps and frequent need for sinus endoscopic surgery is characteristic of this group of patients.<sup>4,7</sup> However, no quantitative study has been published comparing the extent and severity of the mucosal inflammation in aspirin sensitive patients with that in aspirin tolerant patients. Current technology offers new diagnostic methods for assessing the paranasal sinus disease, including computed tomographic (CT) scanning. CT scanning is the best means of visualising the anatomy and pathology of the sinuses, and allows assessment of the extent of sinus involvement and measurement of mucosal

thickening in all sinuses including the ostiomeatal complex. We have recently introduced and validated a semiquantitative scoring system to assess the extent of sinus mucosal involvement,<sup>8</sup> which is a modification of the scoring scale described by Newman *et al.*<sup>9</sup> Using this CT scoring system, we have studied a group of 13 aspirin sensitive patients with chronic rhinosinusitis and nasal polyps and 11 patients with chronic rhinosinusitis and nasal polyps, but without intolerance to aspirin (Kowalski *et al*, in preparation). Both groups of patients had rhinosinusitis of similar duration and had undergone a similar number of nasal polypectomies. CT analysis showed signs of mucosal disease including mucosal swelling, hypertrophy, polyp formation in the sinuses, and obstruction of the ostiomeatal complex in both groups of patients. However, the extent of the disease, assessed by the scoring scale, was significantly higher in aspirin sensitive patients than in those with no sensitivity to aspirin. The differences were also significant for individual sinuses. This study has therefore shown, for the first time in a quantitative manner, that the extent of hyperplastic rhinosinusitis was greater in aspirin sensitive than in aspirin tolerant asthmatic subjects with rhinosinusitis of similar clinical severity.

## Are the mechanisms of mucosal inflammation in the upper airways of aspirin sensitive and aspirin tolerant patients different?

It is not clear if the basic mechanism of chronic airway inflammation in aspirin sensitive patients is different from that in aspirin tolerant patients with chronic rhinosinusitis and nasal polyps. Nasal eosinophilia is a prominent feature of aspirin sensitive rhinosinusitis although quantitative differences from allergic rhinitis could not be consistently demonstrated.<sup>10</sup> Although nasal polyps in aspirin sensitive patients are typically eosinophilic, their histological appearance does not seem to differ from polyps removed from aspirin tolerant patients.<sup>11</sup> Intranasal challenge with aspirin results in an influx of eosinophils into the nasal lavage fluid, with concomitant increases in the concentration of eosinophilic cationic protein (ECP) and tryptase indicating specific activation of eosinophils and mast cells, respectively, in aspirin sensitive patients only.<sup>12</sup> On the other hand, analysis of nasal lavage fluid showed no differences between the mean concentrations of vascular protein (albumin), secretory proteins (lactoferrin and lysozyme), or other inflammatory mediators (histamine, PGD<sub>2</sub>,

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LTC<sub>4</sub>/LTD<sub>4</sub>) in basal secretions of both aspirin sensitive and aspirin tolerant patients.<sup>15</sup> However, oral or nasal challenge with aspirin resulted in a significant increase in the LTC<sub>4</sub>/LTD<sub>4</sub> concentration in nasal washes, indicating activation of the lipoxygenase pathway of arachidonic acid metabolism in the nasal mucosa.<sup>13,14</sup> In contrast to earlier immunopathological examinations which showed that nasal polyps and sinus tissue from asthma sensitive patients were indistinguishable from those from aspirin tolerant patients,<sup>10,11,15</sup> recent studies of biopsy specimens from nasal polyps have provided new data.<sup>16,17</sup> Although aspirin tolerant allergic and non-allergic patients (most with aspirin sensitivity) had similar numbers of inflammatory cells in the polyp tissue (with the exception of CD3+ T lymphocytes), both groups had distinct cytokine profiles. Interleukin 4 expression was predominant in the polyps of allergic subjects and expression of interferon gamma (IFN $\gamma$ ) was characteristic of those from non-allergic subjects. Moreover, sensitivity to aspirin was strongly correlated with non-allergic polyps and with production of the non-allergic profile of cytokines including IFN $\gamma$ . These data suggest that the basic mechanism of chronic airway inflammation may be different in aspirin sensitive and aspirin tolerant patients with hyperplastic rhinosinusitis.

The immunological mechanisms underlying the more severe rhinosinusitis and recurrence of nasal polyps in aspirin sensitive patients remain unclear. In addition to enhanced inflammatory cell recruitment resulting from possible enhanced generation of chemotactic factors in the mucosa, delayed programmed cell death (apoptosis) may account for the increased accumulation of inflammatory cells in nasal polyp tissue. Because of their abundance in nasal polyps, eosinophils seem to be the primary inflammatory cells regulating and perpetuating inflammation.<sup>18</sup> It has been suggested that eosinophils cultured from nasal polyps have increased survival because of delayed apoptosis compared with cells from control mucosa. In order to elucidate the possible involvement of delayed apoptosis in the pathogenesis of nasal polyposis in aspirin sensitive patients we used the TUNEL technique to detect apoptotic cells in paraffin sections of nasal polyps from 16 aspirin sensitive patients and 36 patients with no aspirin sensitivity.<sup>19</sup> Using a computerised image analysis system we found that the number of eosinophils was significantly increased in nasal polyps from aspirin sensitive patients compared with aspirin tolerant patients. On the other hand, the number of apoptotic cells was significantly lower in aspirin sensitive patients (mean 5.5 (SE 1.5) cells/mm<sup>2</sup>) than in either atopic (18.7 (3.8) cells/mm<sup>2</sup>) or non-atopic (21.3 (5.2) cells/mm<sup>2</sup>) patients with nasal polyps. We therefore concluded that enhanced nasal eosinophilia, as well as severity and persistence of nasal polyposis, might be related to impaired apoptosis in aspirin sensitive patients. Eosinophil apoptosis is controlled by several cytokines and it is conceivable that the

abovementioned cytokine imbalance may be involved in the pathogenesis of the persistent eosinophilic inflammation observed in the airway mucosa of aspirin sensitive patients.

We have recently reported that nasal polyp epithelial cells cultured from aspirin sensitive patients generated significantly less prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), both spontaneously and after stimulation with calcium ionophore, than cells cultured from polyps from aspirin tolerant patients.<sup>20</sup> Our observation is further supported by the study of Picado *et al*<sup>21</sup> who found lower expression of cyclo-oxygenase 2 in nasal polyp tissue from aspirin sensitive patients than in polyp tissue from aspirin tolerant patients. Because PGE<sub>2</sub> has significant anti-inflammatory activity, including an inhibitory effect on eosinophil chemotaxis and activation, we speculated that an intrinsic defect in local generation of PGE<sub>2</sub> may contribute to the more severe eosinophilic inflammation in aspirin sensitive patients.

### Is the management of chronic rhinosinusitis and nasal polyps different in aspirin sensitive patients?

Although aspirin is only one of many triggers exacerbating symptoms of rhinosinusitis and asthma in these patients, the presence of aspirin sensitivity heralds severe and protracted disease of the respiratory tract, requiring comprehensive management of all components of the syndrome.

The management of aspirin sensitive rhinosinusitis does not differ from treatment of other forms of this disease but there are several important points which have to be taken into account. Patient education and careful avoidance of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is very important since aspirin may cause severe asthmatic attacks in a significant proportion of patients admitted to the intensive care unit. Careful management of chronic rhinosinusitis is essential and may be a prerequisite for the improvement in bronchial symptoms.<sup>22</sup> Traditional medicines such as nasal decongestants and antihistamines give limited relief in these patients, but topical steroids seem to be very effective. In many patients various surgical procedures may be needed to relieve chronic sinusitis and to remove nasal polyps. CT imaging for assessment of the extent of the sinus disease may also be useful. Depending on the stage of the disease, surgery consists of polypectomy, functional endoscopic sinus surgery, or ethmoidectomy in resistant cases. However, because surgery does not affect the underlying inflammatory component of the disease, medical treatment with topical steroids is also necessary following surgery.

A new approach to the treatment of asthma sensitive rhinosinusitis/asthma is to give aspirin orally after desensitisation since these patients can be desensitised by repeated challenges with aspirin and can then take the drug with impunity.<sup>23</sup> In a subgroup of patients ingestion of aspirin after desensitisation may result in alleviation of nasal symptoms and decreased recurrence of nasal polyps.<sup>24,25</sup> Desensitisation

can be also achieved after repeated intranasal application of lysine aspirin. It has been reported that intranasal desensitisation and prolonged treatment with soluble intranasal aspirin has a beneficial effect on the symptoms of chronic rhinosinusitis. Moreover, Patriarca *et al*<sup>26</sup> reported that the weekly use of intranasal aspirin after desensitisation in patients with aspirin sensitivity significantly reduced the recurrence rate of nasal polyps compared with placebo. Interestingly, similar results were obtained after treatment with intranasal aspirin in aspirin tolerant patients with nasal polyps.

Leukotriene receptor antagonists and synthesis inhibitors have been shown to be of clinical benefit in patients with aspirin sensitive asthma.<sup>27</sup> A preliminary study suggests that anti-leukotriene drugs may also be effective in the management of chronic rhinosinusitis in aspirin sensitive patients.<sup>28</sup>

In conclusion, available data suggest that chronic rhinosinusitis and nasal polyposis in patients with aspirin sensitivity differ with respect to both severity and basic pathophysiology from upper airway disease in aspirin tolerant patients. These differences should be taken into account when planning the management of rhinosinusitis in aspirin sensitive patients.

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