

Management of nasal polyps in 'aspirin sensitive asthma' triad

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Purpose of review

Aspirin-sensitive asthma (ASA) triad is a challenging picture presenting to both the otolaryngologist and the respiratory physicians. Patients present with severe nasal polyposis with a high propensity to recur despite the modality of treatment – medical or surgical. They also often have poorly controlled severe adult onset asthma. We reviewed the scientific literature, focusing on the outcomes of these treatment modalities in the management of nasal polyposis in ASA triad.

Recent findings

Although initial work described by Widal on the subject continues, in the last decade a number of prospective and retrospective studies on outcomes after aspirin desensitization as well as surgery have been reported. The extent of surgery has also been addressed in some of these studies. Medical as well as surgical treatments have a role but there has been increasing evidence to support the role of aspirin desensitization in achieving long-term control of this condition.

Summary

Overall, with the limitation of data, it appears more is better in patients with ASA and nasal polyposis. There is a lack of level 1 evidence in the proposed treatment modalities. Questions on extent of surgery and dosage as well as length of aspirin desensitization require further research with minimally biased controlled studies.

Keywords

aspirin, asthma, nasal polyposis

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Introduction

The aspirin-sensitive asthma (ASA) triad is a clinical picture which presents with aspirin intolerance, chronic rhinosinusitis with nasal polyposis and intrinsic bronchial asthma as first described by Widal in 1922 [1]. Max Samter, an American immunologist, in the 1960s revisited the association and proposed the possible pathogenesis and hence often has his name associated with the triad (Samter's triad or syndrome) [2]. The condition is also often referred to as aspirin-exacerbated respiratory disease (AERD).

Although ASA triad is a clinical diagnosis, it can be confirmed by oral, inhaled, nasal, or intravenous placebo-controlled provocation tests with increasing doses of aspirin [3–6]. Patients with this triad present to Ear, Nose and Throat (ENT) with symptoms related to their nasal polyps and poor asthma control. The management of these patients can be quite challenging as they generally are refractory to traditional treatments, they have a they notable tendency to early relapses and their asthmatic symptoms may become more difficult to control with time. Nasal polyps in aspirin intolerant patients are generally more recalcitrant to both medical and surgical treat-

ment. We aim to review the outcomes of medical and surgical treatment of nasal polyps in patients with ASA.

Clinical characteristics

The incidence of aspirin intolerance in the general population ranges from 0.6 to 2.5% and in adult asthmatics varies from 5 to 10% in mild asthmatics and up to 24% in patients with more severe asthma [1,7]. It is more frequent in women than in men, unusual in children, adult onset with an average age of 30 years. Rhinorrhoea and nasal congestion appear first, subsequently complicated by nasal polyposis. These patients may present with an incomplete triad initially, with nasal polyps as the first indication of aspirin intolerance. Asthma and aspirin hypersensitivity can develop 2–15 years later. Once developed, aspirin intolerance remains throughout life, although sporadic disappearance of intolerance has been reported [8].

Aspirin intolerance is associated with intolerance to other nonsteroidal anti-inflammatory drugs (NSAIDs) in 68% of patients [9]. Typically, patients with ASA triad suffer from a usually difficult to severe attack of asthma within 30–90 min of ingesting aspirin or other NSAIDs, usually

accompanied by nasal symptoms, rhinorrhoea and/or nasal congestion [10]. Diagnosis of this condition is made on clinical presentation of the triad components with adult onset asthma, aspirin sensitivity and nasal polyposis.

Pathophysiology of aspirin-sensitive asthma triad

It has been demonstrated that aspirin intolerance is not an immunologically mediated reaction [1]. The pathophysiology lies in abnormal interaction of the drug with the eicosanoid pathway responsible for arachidonic acid metabolism. Szczeklik and Stevenson [11] proposed that, in patients with ASA triad, inhibition of cyclooxygenase (by aspirin or NSAID) leads to altered metabolism of arachidonic acid, resulting in severe bronchospasm and nasal symptoms. Oral or nasal challenge with aspirin in ASA triad patients induces significant peptidoleukotriene release into the nasal lavages with concomitant nasal symptoms [12]. As peptidoleukotriene synthesis inhibitors or receptor antagonists can significantly decrease or inhibit these reactions in the lower and upper airways, it is suggestive that leukotrienes may play a crucial role in the pathophysiology of ASA-induced reaction [13].

Medical management

The principle of medical treatment for the nasal polyposis is targeting the underlying pathophysiology leading to polyp formation. Marked eosinophilia with persistent inflammation has been described in bronchial and nasal specimens from airways of patients with ASA [14,15]. Chronic eosinophilic rhinosinusitis results in the development of nasal polyps which are difficult to treat [16]. Steroids are effective in reducing the inflammatory process with reduction in polyp size.

Intranasal steroids (INSs) have very few adverse effects and are widely used as a first-line treatment of nasal polyps. Patients with limited polyp disease are good candidates for INSs providing an excellent maintenance therapy to control development of recurrence [17]. Fluticasone and budesonide have been shown to be effective in treating nasal polyps in ASA, with improvement in sinonasal symptoms and polyp size when used over a period of 4 months, particularly when nasal passages are patent [18]. A similar effect has been objectively demonstrated by Ogata *et al.* [19] with marked reduction in eosinophilia in nasal polyps in ASA patients on INS treatment.

'Medical polypectomy' is performed by systemic administration of steroids and symptomatic relief has been noted, especially with regaining the sense of smell [20]. Systemic steroids are frequently used for short

Key points

- Patients who suffer with aspirin-sensitive asthma (ASA) triad have severe nasal polyposis that is often refractory to medical and surgical treatment modalities.
- Nasal polyposis in ASA triad needs a combination of treatment regimes, beginning with medical treatment, and aspirin desensitization therapy should be considered.
- There is a need for further prospective long-term and level 1 evidence studies to answer questions as to extent of surgery and dosage of aspirin in desensitization as well as length of treatment.

periods to shrink large polyps to allow effective INS therapy. Nores *et al.* [21] demonstrated that systemic steroids were successfully used in preventing 68.5% of patients with nasal polyposis from undergoing surgery. Recurrences after medical treatment are common, and continuous use of systemic steroids has its side-effects. Surgery remains the next course of treatment in patients who fail to respond to systemic steroids.

A recent case series described the potential use of methotrexate in treatment of patients with ASA. They witnessed a dramatic reduction in nasal polyposis in patients with ASA during treatment with methotrexate for their steroid dependent asthma [22]. Although a promising and interesting alternative line of treatment, considerably greater research needs to investigate this line of treatment before it can be recommended as standard treatment in these patients.

Excessive peptidoleukotriene release via abnormal eicosanoid pathway is noted in the aspirin-induced reaction in ASA patients. Antileukotriene agents, when used in ASA, have demonstrated clinical improvement on endoscopy findings of nasal polyps [23]. A recent review on use of antileukotrienes in ASA concluded positive effects when used in combination with other drugs during medical treatment and when used during the pre-operative and postoperative periods [24]. Antileukotrienes were noted to act synergistically when used with steroids as well as antihistamines. Perioperative use demonstrated improvement in asthma outcomes as well as nasal symptomatology when used preoperatively and a reduction in recurrence when used postoperatively. The review concluded that some studies had minor levels of evidence and recommended more controlled studies. Overall, it was recommended that leukotriene antagonists should be considered in the management of nasal polyps as well as in the management of asthma in patients with ASA.

Prostaglandin E2 has an anti-inflammatory effect on the activation and chemotaxis of eosinophils. Its formation

appears to be depressed in patients with aspirin intolerance when compared with normal controls as well as in aspirin tolerant patients with polyps [25]. This causes an increased 5-lipoxygenase activity, resulting in cysteinyl overproduction, which is pivotal to bronchoconstriction and mucosal inflammation in ASA patients [11]. It is clear that aspirin triggers this cascade, and in 1984 the use of aspirin desensitization was first described and showed clinical improvement of the underlying inflammatory airway disease [26]. Although the exact mechanisms of this remain unclear, during aspirin desensitization, short-term and long-term studies have shown a reduction in leukotriene (LTB) 4 synthesis [27], decreased levels of LTC 4 and histamine in nasal lavage fluid [28], reduction in plasma histamine and tryptase [29], reduction in urinary LTE 4 levels [30], and marked reduction in airway responsiveness to LTE 4 but not histamine after aspirin desensitization [31]. Clinical improvement with short-term and long-term aspirin desensitization therapy has been shown in a number of studies with outcomes of reduction in the systemic and topical steroid requirements, decrease in recurrence of nasal polyps, need for further revision sinus surgery, and improvement in severity of asthma and sense of smell [32–35]. It is important to note that aspirin desensitization is a long-term treatment, as symptoms return when this is discontinued [34]. There is evidence that, when used in line with current guidance, aspirin desensitization therapy is safe and effective in the treatment of AERD [36]. Aspirin desensitization should therefore be considered in the management of both the lower and upper airway inflammation in ASA triad patients.

Surgical treatment

Surgical intervention in the treatment of nasal polyps is considered in patients who fail to improve with maximal medical treatment. Although surgical treatment by simple polypectomy relieves symptoms of nasal blockage, it is fraught with high recurrence rates [37].

Endoscopic sinus surgery (ESS) with polypectomy allows removal of the nasal polyps, clearance of polypoid disease in the ethmoids and opening of the larger sinus ostia. Improving sinus ventilation and mucociliary clearance is paramount in the treatment of chronic rhinosinusitis (CRS) with or without polyps. There are a number of retrospective studies assessing post-ESS outcomes in patients, comparing ASA patients with aspirin tolerant asthma (ATA) patients with CRS and nasal polyps. All have found ESS to have a beneficial effect on the sinonasal and asthma symptomatology on objective assessment of forced expiratory volume in 1 s values and need for inhaled corticosteroid spray [37,38,39^{••},40]. Smith *et al.* [38] demonstrated that ASA patients showed the greatest improvement in endoscopy scores in comparison to their aspirin tolerant counterparts. They also found

that, although the presence of ASA adversely affected the total quality of life (QOL) improvement in patients treated with ESS, this group still experienced a significant improvement in QOL scores. Awad *et al.* [40] explored the asthma outcomes comparing ASA with ATA patients after ESS. Although ESS helped both groups of patients, ASA had statistically significantly better results compared with ATA patients in asthma severity scores and decreased need for inhaled corticosteroids. These results are, however, contradictory to a previous study by Batra *et al.* in 2003 [37], which found that the subset of aspirin tolerant patients had statistically better outcome for sinonasal symptoms and pulmonary function testing than aspirin sensitive patients. Both studies are retrospective and with very similar methodology. Although the former has twice the number of patients, the contradictory results suggest the need for prospective controlled studies.

The study by Awad *et al.* [39^{••}] found that ASA patients had more extensive sinonasal disease than ATA patients. Both groups showed statistically significant improvement in sinonasal symptoms after ESS. The difference between the two groups was statistically significant for patients' computed tomography (CT) improvement, with worse CT scores being seen in ASA patients. In the follow-up period of this study, only 63.4% of ASA patients at 18 months had CT improvement in comparison to 96% of ATA patients. However, it is not possible to postulate whether the CT scan would eventually translate into symptoms in this group of patients. Amar *et al.* [41] performed a retrospective outcome analysis on ASA patients who had undergone ESS and compared these with a control group of patients with CRS but not ASA. It was found that ASA patients had more extensive involvement radiologically and required a large number of repeat ESS procedures, suggesting that these patients responded less well to surgery.

There is increasing evidence that aspirin desensitization after ESS in ASA patients may reduce the need for revision ESS. A retrospective study of 15 patients looking at aspirin desensitization versus non-aspirin desensitization after ESS in ASA patients found that no patients in the aspirin desensitization group needed revision ESS at 2 years, whereas eight of 10 non-aspirin desensitization patients required additional revision during the follow-up period ($P = 0.003$) [42[•]].

McFadden *et al.* [43] performed a retrospective review of ASA patients over an 11-year period, looking at extent of surgery and the need for revision ESS. They found that six out of the 16 patients who had limited ESS and none of the nine patients who had radical ESS needed revision surgery. This suggests that radical surgery may be beneficial to ASA patients. In 1997, Jankowski *et al.*

[44] prospectively compared patient satisfaction using a visual analogue scale and the recurrence rate of nasal polyps in 39 patients who had radical ethmoidectomy (nasalisation) with 37 patients who underwent functional ethmoidectomy by two different surgeons. This was performed in patients with diffuse or severe nasal polyps. They found that the nasalisation group had a recurrence of 22.7 versus 58.3% in the functional ethmoidectomy group, which was statistically significant. The overall functional benefit was also noted to be statistically significantly higher in the nasalisation group, suggesting that treatment of nasal polyposis with complete ethmoidectomy leads to better long-term results than incomplete ethmoidectomy. Although showing promise, these results need updating with a robust randomised controlled study with minimal bias. Overall, taking into account the limitations of the published data, it appears more is better in patients with ASA and nasal polyposis.

Conclusion

ASA patients tend to have florid nasal polyposis (clinically and radiologically) and often are refractory to both medical and surgical treatments. Unfortunately, most of the studies evaluating the data on treatment outcomes in ASA triad are retrospective with short-term follow-up. Medical management remains the primary option of treatment for nasal polyposis in patients with ASA as well as ATA. This should be with multimodalities including short-term systemic steroids, long-term intranasal steroids and leukotriene antagonists. Response is seen with improvement in sino-nasal as well as respiratory outcomes. There is increasing evidence suggesting that aspirin desensitisation is beneficial in reducing sinonasal symptoms, respiratory control and the recurrences post surgery. Patients who are refractory to optimal medical therapy should be considered for ESS. The limited evidence suggests that a more radical surgery is beneficial to patients with severe or diffuse nasal polyposis. There is lack of level 1 evidence and prospective long-term follow-up studies assessing the treatment of nasal polyposis in ASA triad patients.

References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 59).

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