

Samter's Triad: pathogenesis, clinical picture, diagnosis, comparison of biological and surgical treatment and the role of aspirin desensitisation

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Summary Samter's Triad (ST), also known as aspirin-exacerbated respiratory disease (AERD), is defined as the correlation of asthma, aspirin intolerance (AI) and nasal polyps (NP). The combination of these symptoms poses a challenge in clinical practice, i.e. difficulties in making diagnosis and managing treatment. The prevalence is estimated at 0.3–0.9% of the general population in the USA, with a slight female predominance, whereas among asthmatic patients, the prevalence is estimated at 10–11%. The most common symptoms of ST are nasal congestion, rhinorrhoea, sneezing, anosmia and sinus opacification with symptoms from the lower respiratory tract due to disease progression. Less common AERD manifestations are cutaneous and gastrointestinal symptoms. The diagnostics is based on a clinical picture, CT findings and provocative aspirin challenge. The treatment strategy is a combination of surgical treatment, aspirin desensitisation and biological treatment, such as Omalizumab or Dupilumab. Among the treatment options, the most beneficial strategy is aspirin desensitisation combined with FESS. The results of Omalizumab and Dupilumab treatment are promising, though they need to be confirmed by further studies. Our aim was to review the latest literature and compare the treatment options and their efficacy. We discussed pathogenesis, diagnosis, clinical picture, surgical and biological treatment options and aspirin desensitisation. **Key words:** asthma, nasal polyps, aspirin, endoscopy, omalizumab, therapeutics.

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Background

Samter's Triad is a correlation of asthma, aspirin intolerance and nasal polyps. The condition is also known under many terms, such as AERD, Samter's Syndrome, Aspirin Induced Asthma, Aspirin Intolerant Asthma, Aspirin Sensitive Respiratory Disease, NSAID Exacerbated Respiratory Disease, Acetylsalicylic Acid Triad, Aspirin Triad, Francis' Triad or Widal's Triad.

The syndrome was first mentioned in 1922 by Fernand Widal and was ignored at first until 1968 [1]. In 1968, the disease started to gain recognition after a German-American Immunologist named Max Samter published research on patients with the above-mentioned correlation of symptoms [2].

Objectives

Our aim of the literature research was to gather current information about the pathogenesis, diagnosis and the treatment options, including surgical management alone and combined with aspirin desensitisation, and biological treatment.

Material and methods

We conducted our literature research within the PubMed, Scopus, Web of Science, Thieme MedOne Otolaryngology, Embase, UpToDate, Scopus, SamtersSociety and Access Medicine electronic databases using combinations of the following key words: Samter's Triad, Aspirin-Exacerbated Respiratory Disease, AERD, Functional Endoscopic Sinus Surgery, FESS, Omalizumab

treatment, aspirin desensitisation. We narrowed the research timeline to the period from 2000 to 2021. The final analysis allowed us to select 30 articles for review.

Pathogenesis

ST is a non-immunoglobulin E (non-IgE) hypersensitivity reaction associated with aspirin or COX-1 inhibitors related to abnormal metabolism of arachidonic acid. The COX pathway involves the creation of PG and thromboxane, whereas the LO pathway serves to create LT and hydroperoxyeicosatetraenoic acid.

There are two different isoforms of COX. Although COX-1 is a continuously expressed enzyme present in most mammalian and most inflammatory cells, COX-2 is an inducible enzyme expressed only in inflammatory cells and is up-regulated by pro-inflammatory mediators such as cytokines and growth factors [3].

Pathogenetic mechanism of Samter's Triad

Aspirin inhibits the COX pathway and diverts arachidonic acid metabolites to the lipoxygenase (LO) pathway. An elevation of the Cys-LT level in the sputum, urine, peripheral blood and exhaled breath after aspirin administration was observed.

By inhibition of COX-1, the production of prostaglandin E₂ (PGE₂) decreases, and this is an important event in the development of an aspirin-exacerbated respiratory reaction. Low levels of PGE₂ lead to increased synthesis of cysteinyl leukotrienes (Cys-LTs). Cys-LTs can induce oedema, bronchoconstriction and mucous secretion into the airways, and LTE₄ induces recruitment of eosinophils to the respiratory tissues in asthmatic subjects. In



addition to increased synthesis of LTs, ST patients have a higher Cys-LTs receptor expression in nasal and bronchial inflammatory cells. We have two known G protein-coupled receptors: Cys-LT type I receptors (CYS-LTR₁) and Cys-LT type II receptors (CYS-LTR₂). Patients show a higher expression of Cys-LTR₁ in inflammatory leukocytes.

The inhibition of COX-2 might lead to a structural change in the enzyme, which results in an increase of Prostaglandin D₂ (PGD₂). PGD₂ is a potent chemoattractant of eosinophils that causes vasodilatation and bronchoconstriction and acts through the PGD₂ receptor of eosinophils. PGD₂ is responsible for the swelling and oedema of respiratory tissue.

Interleukin 4 (IL-4) and interferon- γ were increased in the tissues of ST patients. IL-4 is closely related to the up-regulation of LTC₄S by mast cells. As a result, these changes lead to excessive LT production, which causes eosinophil chemotaxis, increased vascular permeability, mucous gland secretion and bronchoconstriction.

The end result for ST patients is a marked increase in the number of mast cells and eosinophils in the respiratory mucosa. Eosinophils secrete several cytotoxic molecules, such as major basic proteins and eosinophilic cationic, causing respiratory mucosal inflammation and injury [1].

Genetic background

Recently, several investigations have suggested the problem of genetic polymorphism. A variation within the genes of the arachidonic acid pathway is responsible for changes in the production and metabolism of inflammatory mediators. The association between HLA-DPB1 locus (single allele of DPB1*0301) was over-expressed in ST patients and was suggested as an independent risk factor for ST development [4]. Polymorphism in such genes as LTC₄S [5], 5-LO, PGE₂ receptor subtype 2, PGE₂ receptor subtype 3 [6], thromboxane A₂ receptor [7] and Cys-LTR₂ [8] have been revealed to be associated with ST. Recently, IL-10, tumour growth factor- β 1, IL-13 and IL-17A gene polymorphism have been reported in patients with ST [9, 10].

Clinical picture

Samter's Triad is the correlation of asthma, nasal polyps, aspirin and other NSAIDs intolerance, the intake of which induces upper and lower respiratory reactions.

Prevalence

The prevalence of aspirin intolerance in the general population is calculated as being from 0.3% to 0.9%, increasing up to 3–20% in asthmatic patients and up to 30–40% in patients suffering from asthma and nasal polyps [1]. It is worth noting that many patients are not aware of aspirin intolerance due to diagnostic difficulties. Studies have shown a slight female predominance in the present case. ST occurs worldwide but is rare in China [11].

Onset of the disease

ST begins at any age, from childhood up to 40 years of age. The median age is 30 years [3, 12]. However, the reduced intake of aspirin in children relevant to the risk of proceeding in Rey's syndrome could be the reason for later onset.

Symptoms

First manifestations are usually seen in the upper respiratory tract and are represented as nasal congestion, rhinorrhoea, sneezing, anosmia and sinus opacification. In addition, patients often suffer from respiratory tract infections. Along with disease progression, the symptoms from the lower respiratory

tract occur. They manifest as laryngospasm, coughing, wheezing and inflammation. From two to five years after the onset of rhinitis aspirin intolerance, asthma start to develop. There are characteristic features of asthma attacks in ST patients – the attack is preceded by aspirin intake, accompanied by rhinorrhoea, conjunctival injection, facial flushing and preorbital oedema. Furthermore, there are less common symptoms that can be seen originating from the gastrointestinal tract (GIT), such as nausea and abdominal pain. Cutaneous symptoms – urticaria and flushing – have also been reported [12]. GIT and cutaneous manifestations are additional to respiratory symptoms, and the occurrence is not common. Some patients also experience airway hypersensitivity reactions after alcoholic beverages, but the mechanism of this reaction remains unknown. At the time of diagnosis, patients have developed nasal polyps. Typically, ST and its symptoms are difficult to manage and treat.

Exacerbating factors

The most common exacerbating factors are viral infections, GERD, physical activity, as well as IgE-mediated reactions to pollen, dust, animals and food. Almost 50% of all instances of ST occur after a viral infection.

Diagnosis

Provocative aspirin challenge

Provocative aspirin challenge is performed by administering increasing doses of aspirin [13, 14]. Four types of provocation tests are used according to the route of aspirin administration: oral, bronchial, nasal and intravenous [5]. Oral challenges are most commonly used and regarded as gold standard methods as the oral route mimics natural exposure, and the test does not require special equipment [15, 16].

Most ST patients have a positive response after taking 30 to 150 mg of aspirin, and the dose should be taken until the cumulative dose of aspirin reaches 500 mg if the patient is not responding according to the EAACI/GA2LEN guideline. If the patient is suspected of having aspirin hypersensitivity, the target cumulative dose can be increased to 1,000 mg [17].

Bronchial challenges with L-lysine aspirin have been used in Korea and Europe. This provocation is safer and faster than the oral route, and the symptoms provoked are restricted only to the bronchopulmonary area. Both tests show similar specificity, though the oral route has a higher sensitivity than bronchopulmonary route [18].

The nasal test is fast, safe and less expensive and may be used in outpatient clinics. However, this test has a lower sensitivity than the oral or bronchial test.

The aspirin challenge test is considered as positive response when the FEV₁ (forced expiratory volume in one second) decreases more than 20%, accompanied by clinical symptoms of rhinorrhoea, bronchial obstruction and conjunctival injection. When no reactions occur within 3 hours after 325 mg of aspirin, the challenge is considered to be negative [17].

All challenge tests should be preceded by a placebo challenge (saccharin lactate administered in gelatine capsules, and these capsules should have an identical appearance to those containing acetylsalicylic acid). This should be carried out to exclude the variability of bronchial responsiveness [6].

Computer tomography

Studies show that patients with Samter's Triad (ST) had higher opacification scores for the ethmoid and frontal sinuses and relatively lower opacification scores for the maxillary sinus. In chronic rhinosinusitis with a nasal polyp without a history of aspirin intolerance (CRS), the opacification scores for the maxillary sinus were higher, than in patients with ST. This is helpful for

differentiating CRS, which could facilitate the planning of treatment strategies without the need for additional laboratory or radiological tests [7].

Treatment

Role of surgical management

Functional Endoscopic Sinus Surgery (FESS) is one of the recommended methods of surgical management in ST patients. The aim of the surgery is more to help establish the course of the disease and symptomatic control than to cure the disease. The surgery is performed to restore sinus ventilation and mucociliary function. In addition, FESS results in a small but significant improvement in lung function, as evidenced by pre- and post-operative spirometer measurements – a marginal improvement in pre- and post-operative spirometry parameters (FEV₁, FVC, FER and PFT) was observed [19, 20]. However, in ST patients, the post-operative outcomes are not as satisfying compared to no-ST patients. In patients who underwent FESS for disease management, the revision surgery rate was 80% [21]. Among the gains from surgical management are improvements in QoL, symptom severity and frequency, radiographic grading, endoscopic scores and asthma severity. An improvement in symptom outcome measurements after surgery was demonstrated in 13 studies and was statistically significant [22]. Surgical treatment is beneficial in ST patients; however, the results of managing disease only with surgery are not sufficiently successful.

Combined therapy – ESS and aspirin desensitisation

The current treatment recommendations in literature advise a combination of surgery and aspirin desensitisation (AD). Studies have proved this strategy to be highly effective [21, 23]. The implementation of AD plays a major role in the medical management of ST in patients after FESS. In a 30-month follow-up, the revision surgery ratio was 9.4% in patients treated with surgery combined with AD, with lower polyp recurrence, improved sense of smell and nasal obstruction [21]. In addition, one revision was associated with discontinuation of aspirin desensitisation. Aspirin desensitisation should be applied several weeks after FESS, with the recommended aspirin dose ranging from 325–1300 mg/day as maintenance therapy [21]. During AD, one of the common side effects is gastrointestinal discomfort, which could be a reason for discontinuation. The benefits of this combined therapy are improvements in the number of sinus infections per year, sinus surgeries needed, olfactory and nasal symptoms, which have an impact on the improvement of patients' quality of life measured via SNOT-22 scores.

Other outcomes after FESS and AD in ST patients

This therapy is also effective in reference to asthma control. 94% of patients reported improvement in asthma symptom scores, the frequency of asthma attacks was decreased in 88.9% of patients in the 12 months after surgery, fewer outpatient visits and inpatient hospitalisations were needed, the use of inhaled and oral steroids decreased, and a significant reduction in asthma severity grade was noted. In the long-term follow-up, patients who underwent ESS and AD are less likely to be on daily prednisolone. The strategy successfully decreased the needed prednisolone dose from 10.6–7.9 mg to 3.8–2.6 mg/daily, due to the strategy, also the doses of systemic, topical and inhaled corticosteroids could be decreased. The lower doses are beneficial for patients and may mitigate the side effects of corticosteroids therapy [23].

Omalizumab in the management of ST

The literature findings referring to biological treatment in ST patients are promising. However, there are limited studies

about Omalizumab treatment which need to be strengthened with larger multicentre and prospective studies. Omalizumab is a recombinant humanised monoclonal antibody which binds the Fcε portion of the IgE antibodies, leading to a reduction in the total IgE level [24]. This prevents an interaction with the high-affinity receptor FcεRI expressed on the surface of the target cells and reduces the expression of the receptor, which results in the suppression of an inflammatory cascade. Along with its usage in ST, Omalizumab is effective in the treatment of different IgE-related diseases, such as allergic rhinitis, food and drug allergies, allergic bronchopulmonary aspergillosis, atopic dermatitis, eosinophilic granulomatosis with polyangiitis or mastocytosis. In one study [24], the efficacy of Omalizumab treatment was seen as an improvement in asthma control with a decreased exacerbation rate and OCS usage, and in lung function tests, an improved FEV₁ score at the follow up and the normalisation of lung parameters in two of three patients included in the study was seen. Other promising findings are improvements in clinical questionnaires, such as the ACT and SNOT-22, meaning better asthma and nasal polyp control, which results in a reduced use of bronchodilator rescue therapies, no need for FESS or surgical nasal polypectomy during the follow-up and a reduction in the number of exacerbations. In addition, a clear reduction of eosinophilic blood count was observed in all patients.

Despite the above-mentioned facts, the results are conflicting. Another study [25] showed no changes in nasal polyps but allergic nasal symptoms, such as sneezing and postnasal drip, and, what is more, asthma symptoms decreased. In this trial reduction of daily ICS and OCS, an improvement in spirometer measurements and a significant reduction of eosinophil, basophil and total IgE plasma count were observed. The frequency of exacerbations also decreased.

Another study [26] confirming the efficacy of Omalizumab described eight patients with ST who had undergone at least one Omalizumab treatment. The results indicate a significant reduction of moderate to severe asthma exacerbation, an increase of FEV₁, reduction of steroids and Short Acting Beta Agonists (SABA) usage and an improvement in the ACT and SNOT22 questionnaires. During the observation time, surgical intervention was not necessary. The biological treatment was also well-tolerated, and there were no discontinuations and no adverse effects.

Despite the promising results, the efficacy of Omalizumab treatment in ST patients requires further studies.

Dupilumab in the management of ST

Dupilumab is a humanised monoclonal antibody, which works through blocking IL-4 and IL-13, leading to a significant decrease in FeNO and eosinophilic inflammation in the sino-pulmonary tract. There was one prospective study on the subject of the usage of Dupilumab on ten patients diagnosed with ST [27]. Six of ten patients had an ST diagnosis confirmed through the aspirin challenge. The pre-treatment median number of the sinus surgeries in this group was three, and the median number of OCS courses was two. In addition, two patients were on chronic aspirin therapy at the time of the study, and three patients had undergone this therapy in the past. The patients received a placebo at first, followed by six months of Dupilumab treatment. During the trial, there were no significant adverse effects, and only one local injection site reaction was observed. The results were promising: the improvement in clinical questionnaires such as the SNOT-22, ACT, Lund MacKay, AQLQ and UPSIT was significant, the total serum IgE decreased from 113–381.8 UI/ml to 31–119.5 UI/ml, and T2 inflammatory biomarkers increased. In addition, two patients were able to discontinue OCS therapy, while eight patients reduced the OCS courses. However, there was no significant improvement in FEV₁. In conclusion, Dupilumab treatment is highly efficacious for symptomatic improvement in ST patients and provides improvement in sinus opacification,

nasal polyp burden and severity of symptoms, which have an impact on improving patients' quality of life.

Discussion

The aim of the article was to perform a systematic literature review and to gather recent knowledge about the pathogenesis and diagnosis of ST. Our other aim was to study and compare the treatment strategies in order to find the most effective method. The article systematises the current state of management of ST, which makes it useful for a large audience, such as GP, laryngologists, allergologists and pulmonologists.

Diagnosis is complicated, and taking a history is of primary importance, sometimes causing diagnostic problems. However, 16% of patients who were clinically suspected of having ST due to a history of asthma attacks, after ingesting aspirin/NSAIDs, could not meet the criteria for ST due to negative aspirin challenge test results. On the other hand, among the patients who had NPs, CRS or asthma without exposure to aspirin/NSAIDs, only forty-three had a positive aspirin challenge test result. The diagnosis of ST could be confirmed only through the provocative aspirin challenge test by increasing the doses of aspirin [1]. Moreover, computer tomography is helpful in detecting ST. In a study by Kim [18], patients with Samter's Triad exhibited a tendency toward higher opacification scores for the ethmoid and frontal sinuses and relatively lower opacification scores for the maxillary sinus; however, diagnosis of Samter's Triad before an aspirin provocation test is difficult.

We studied the role of pharmacological, surgical and biological treatments. Literature findings [22] indicate the role of functional endoscopic sinus surgery as a support for other treatment strategies. Without a doubt, surgical management can provide improvement in SNOT scores, RSDI and CSS, asthma severity scores and olfactory function. After surgical management, the need of hospitalisations, ER visits and the dosages of inhaled and oral steroids decreased. Beside these advantages, it is important to highlight that patients with ST may need more frequent revision surgery and that the extent of the surgery is not standardised – further studies to determine the role of surgical treatment is essential, although some authors [28] emphasise the tendency to relapses of the disease and suggest conservative treatment as the optimal management of ST.

The studies show [29] that a combination of surgery and AD provide a synergistic beneficial effect for ST patients. The improvement was measured by SNOT-22 scores after FESS one and four weeks after surgery and showed an improvement at all time points when ASA desensitisation was added to surgical treatment. Among the other benefits from combined therapy, the recurrence of polyps was decreased. The best time to perform ASA desensitisation is immediately after FESS. There is lack of information about the duration and maintenance dosage.

The other literature findings [2], the present role of aspirin desensitisation is crucial for managing ST. Beneficial effects from this therapy include improvement in upper and lower respiratory tract symptoms with reduced use of corticosteroids, slower regrowth of polyps and a reduced need for surgical treatment. However, 22% of the studied patients discontinued treatment because of side effects or no observed beneficial effects.

Other studies present [24] Omalizumab as an alternative treatment option. The effectiveness of biological treatment was proven in patients with ST. This treatment resulted in improvement in asthma control, a decreased exacerbation rate, a reduced need of OCS use and an improvement in FEV₁. Furthermore, during the follow-up, there was no need to perform surgical treatment. However, the data is limited, and a randomised clinical trial should be performed to confirm the results. Other authors provide conflicting results [26], i.e. no changes in nasal polyps after Omalizumab treatment.

The results after Dupilumab treatment are promising [27]: an improvement in clinical questionnaires (SNOT-22, ACT, Lund MacKay, AQLQ and UPSIT) was observed, the total serum IgE decreased, there was a reduced need of oral corticosteroid usage. It is worth noting that in comparison to Omalizumab treatment, an improvement in FEV₁ was not observed.

The diagnosis of Samter's Triad is challenging in clinical practice. According to the current state of knowledge, the best diagnostic is the oral aspirin provocative challenge, confirmed by computer tomography. Among the treatment options, the most beneficial strategy is aspirin desensitisation combined with FESS. The results of Omalizumab and Dupilumab treatments are promising; however, they need to be confirmed by further studies.

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