Introduction

The triad of nasal polyps, aspirin intolerance and asthma was first described by Widal et al. in 1922 and again by Samter in 1968 what gave the name of this clinical entity. Asthma usually occurs first, followed by aspirin intolerance, and then nasal polyps. In many cases, only two parts of the triad are present [1, 2].

The exact mechanism of the disease is unknown but it is considered to be due, at least in part, to a disturbance of eicosanoid biosynthesis. Eicosanoids are rapidly synthesized and released products of arachidonic acid (AA) metabolism mainly via the cyclooxygenase (CO) and lipoxygenase (LO) pathway and, to a small extend, via the epoxygenase pathway (EO). The conversion of AA to prostaglandin (PGs) and thromboxanes (TXs) involves the CO pathway. The conversion of AA to leukotriens (LTs) and hydroxyeicosatetraenoic acid (HETEs) is via the LO pathway. Aspirin competes with AA by irreversibly binding to the cyclooxygenase active site, thereby shifting AA to the LO pathway. The inhibition of cyclo-
oxygenases by aspirin results in the diversion of arachidonic acid products toward the lipo-oxygenase pathway, resulting in overproduction of leukotriens and other mediators, and a reduction of anti-inflammatory prostaglandins [1–4]. However, in some scientists opinion, increased production of LTs apparently does not depend on the acetylsalicylic acid (ASA) effect alone. Even in the absence of ASA, the baseline AA metabolic rate of peripheral blood monocytes of patients with ASA-sensitive respiratory disease is higher than those of

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normal controls [5–8]. Jurgens et al. found that monocytes of ASA-sensitive patients produce larger amounts of both TXs and LTs compared to normal individuals. This indicates a generalized acceleration in the AA metabolic rate through both the CO and LO pathways in these patients. They also found subsequent ingestion of ASA resulted in a significant decrease in TX and a significant increase in cysteinyl LT release and that this was clinically associated with bronchospasm [9]. Thus ASA inhibited CO, shunted AA through the LO pathway, and resulted in the hypersecretion of cysteinyl LTs. These LO products are potent bronchoconstrictors and also increase vascular permeability, resulting in the airway edema and secretions associated with acute asthmatic attacks as well as the nasal symptoms seen in the Aspirin Triad (AT) syndrome. This is thought to cause an exacerbation of asthma and formation of nasal polyps [4, 5, 8–10]. The HLA allele DPB1*0301 may represent the aspirin exacerbated respiratory diseases (AERD) phenotype, and that patients with this allele displayed typical clinical characteristics of Samter’s triad with lowered FEV1 levels and increased prevalence of rhinosinusitis with nasal polyps [5, 10–12]. Another potential AERD genetic biomarkers include leucotriene C4 synthase (LTC4S), ALOX5, CYSLT1, PGE2, TXA2R, TBX2, MS4A2, IL10-1082A > G, ACE-262A > T, CRTH2-466T > C, together with the four-locus single nucleotide polymorphism (SNP) set B2ADR46A > G, CCR3-520T > G, CysLTR1-634C > T and FCER1B-109 > C [5, 13–17].

This disease represents the most aggressive form of nasal polyps. Nasal polyps occur in 36–96% of patients with aspirin intolerance. Conversely, of all patients with nasal polyps 12.8% have aspirin intolerance [3, 4].

Thus, the upper and lower respiratory disease of aspirin triad patients involves a number of complex mechanisms operating at the level of their respiratory mucosa. This results in mast cell activation, eosinophilia, and the production of chronic inflammatory mediators that worsens with ASA ingestion. These mechanisms appear to be distinct from those seen in other patients with chronic rhinosinusitis with nasal polyps (CRS/NP) but without ASA-sensitivity [2–5].

Patients with Samter’s triad generally tend to have more severe symptoms of nasal polyposis and asthma, as well as rhinosinusitis, than do patients without the triad. When their chronic sinusitis fails to respond to aggressive medical management, surgical intervention is indicated and has been found in a number of studies to reduce the severity of the asthma, but their postoperative course is often complicated by a recurrence of nasal polyps [3–5].

The aim of the study was to present actual tendencies in the management with nasal polyps in the course of Samter’s triad.

### Epidemiology

According to Varghese at al. the presence of nasal polyps in aspirin sensitivity patients may be as high as 14–22% and the chronic rhinosinusitis from 0.7 to 2.6% [18].

Jenkins et al. found that nasal polyps prevalence rates are 21% and 5% for asthmatic adults and children, respectively, when examining primarily unblended oral provocation tests in a systematic review of 66 articles on aspirin exacerbated asthma (AEA). The prevalence was dependent on the method used to diagnose AEA, with patients histories alone giving a much lower prevalence rate of 2.7% in adults and 2% in children [19].

A database study from Poland in which 12,971 adults were randomly selected showed a prevalence of AEA of 0.6% in the general population and 4.3% of subjects with a known diagnosis of asthma. With nasal polyps patients, aspirin sensitivity may be as high as 14–22%, and with chronic rhinosinusitis, it is 0.7–2.6% [20].

Aspirin intolerance may be widely underdiagnosed – in the European network of aspirin induced asthma, 18% of participants were unware of aspirin sensitivity before undergoing unblended aspirin provocation tests [3, 4, 21].

Rhinorrhea and nasal congestion are usually the first symptoms of AEA and are commonly refractory to pharmacologic therapy. It becomes perennial and more difficult to treat and then becomes associated with anosmia, recurrent and chronic sinusitis, and nasal polyposis [3, 4, 21, 22].

### Diagnosis

Taking the medical history is of primary importance during the first visit to the doctor, who must attempt to establish the link between salicylate contact and the occurrence of the symptoms. This is only successful if they occur at close intervals. The doctor must therefore ask whether asthma, skin symptoms, swelling of the nasal mucosa, gastrointestinal symptoms or the (very rare) cardiovascular shock have occurred immediately after salicylate consumption. Polyps in the nose and nasal sinuses occur later and grow slowly; the decisive clue is than provided by rapid and repeated recurrence after operative removal.

The accepted diagnostic gold standard is the exposure on aspirin or provocation test. However, these can only confirm or exclude the suspicion for rapid reaction such as asthma. Long-term developments such as polyps cannot be adequately followed. Acetylsalicylic acid is normally administered orally or nasally. Emergency precaution should be taken, as there may be violent reaction, such as asthma. This includes possibility of observation in hospital and follow-up care. This diagnostic measure requires the proper equipment and is demanding for the personnel [3–5, 23].

Diagnosis can also be based on imagine techniques, including computed tomography (CT) for polyps and tests of lung functions to measure obstruction after exposure or provocation. Triad patients usually have a more extensive sinus involvement at initial presentation and are twice as likely as nontriad patients to report a history of previous nasal surgery. CT scans evaluation and the number of previous nasal surgeries have often been cited as a useful prognostic indicators. As evidenced, the mean radiologic grades of triad patients are significantly higher than those of nontriad patients. Of note is that the anterior and posterior ethmoid sinuses are the most extensively involved sinuses in both groups of patients, but more so in the triad patients [24–27]. As Richtsmeier explained, the pathogenesis of maxillary and frontal sinusitis shows a central role of the anterior ethmoidal complex. The higher radiologic
grades of the ethmoid sinuses in the triad would explain the grater level of triad patients involvement of the frontal and maxillary sinuses in that same group [28]. The nontriad patients, who have a much lower degree of ethmoid involvement, also have a lower degree of frontal and maxillary involvement [26–28].

Functional ex vivo tests are based on the detection of indicators in the patient’s tissues exposed to the test substances. The following systems are currently commercially available.

- Measurement of the released quantity of LT from prepared basophils. This corresponds to the LOX-dependent metabolic pathways.
- Measurement of the lysozyme – associated membrane protein CD 63 by flow cytometry. This has been reported to occur on degranulating basophiles. The measurement of enriched basophiles is a less suitable approach to diagnose salicylate intolerance.
- An extended functional eicosanoid test (FET) can be used to measure the eicosanoids LT and PG released after exposure to salicylates or other substances. This gives a more quantitative measurement of the metabolic pathway of LOX and COX under both normal conditions equivalent to the disease, together with the dependence on symptoms such as polyposis, rhinitis, and others [29–32].

The newer functional tests are useful for unclear cases and when there is no close correlation in time between the symptoms and exposure or provocation on aspirin. These tests are absolutely indispensable when exposure or provocation is unacceptable because of the circumstances and the patient’s expected reaction, or because of contraindications such as infection or bronchial asthma [29–32].

**Differential diagnosis**

In the differential diagnosis all types of chronic rhinosinusitis (chronic rhinosinusitis without nasal polyps and chronic rhinosinusitis with nasal polyps) should be taken under consideration. Especially, correlation between chronic rhinosinusitis and presence of allergy should be considered in these cases [3–5].

**Treatment**

**Prevention**

The most reliable form of prophylaxis and therapy is to interrupt treatment. It is particularly important to avoid COX-1 inhibitors. However, some patients react with the same symptoms to very high dosages of paracetamol, used as a substitute. In these cases, low-dose buprenorphine or tramadol, other non-steroid anti-inflammatory drugs (NSAID) must be prescribed [3–5, 33, 34].

NSAID that are highly selective for COX-2, for example, celecoxib and rofecoxib, do not cause acute exacerbation of asthma in AEA [3, 4, 35]. If highly sensitive patients interrupt treatment they must also avoid cosmetics and food with high salicylate content, particularly spices and industrially processed food [3–5, 34].

**Drug treatment**

The guidelines used to treat and manage AEA are no different from those used to treat moderate to severe persistent aspirin tolerate asthma (ATA). Individuals with AEA occasionally require systemic corticosteroids in addition to their regular maintenance therapy.

The most active drugs are corticosteroids, as one of their activities to inhibit the catalysis of the formation of arachidonic acid by phospholipases, the precursor of the responsible eicosanoids. Steroids treatment can be topical or systemic [3, 4, 33–35].

Leukotriene inhibitors, such as zileuton, which inhibits 5-LO, and leukotriene receptor antagonists, such as montelukast and zafirlukast, are used to treat AEA. However, ATA and AEA subjects on leukotriene inhibitors have similar clinical outcomes, and urinary LTE4 cannot be used to determine responses to these medications [36–38]. AEA subjects with the C allele appear to have a better response with leukotriene receptor antagonists [36–38].

**Surgical treatment**

Little has been reported in the literature about the prevalence of Samter’s triad among patients who are treated with functional endoscopic sinus surgery (FESS). In the paper of Kim and Kountakis the prevalence of these patients among all undergoing FESS was: 4.8% among all patients undergoing FESS – 9.4% for patients with nasal polyps, 16.9% for patients with asthma, and 25.6% for patients with both nasal polyps and asthma [39].

Surgical treatment of severe sinusitis in aspirin triad patients does not worsen their asthma and has been helpful in decreasing steroid dependence and improving asthma and sinus symptoms.

Although numerous publications have focused on the overall outcome of FESS, very few have explicitly studied the impact of Samter’s triad on the success of these procedure. In one of the few studies looking at Samter’s triad, Schaitkin et al. recorded a 91% symptomatic improvement at a 4-year follow-up of non-aspirin triad patients having undergone FESS. Eighteen percent of these patients were completely symptom free. Triad patients reported only an 82% improvement, with 0% reporting complete resolution of symptom. Furthermore, 36% of ASA triad patients required revision surgery during the follow-up period versus 23% for non-ASA triad patients [40]. McFadden et al. reported that if antral and sphenoid disease is present in a triad patient, a more radical approach such as Caldwell-Luc surgery is indicated rather than a FESS [40, 41].

Despite the use of these surgical procedures recurrences are common, and up to 60% of patients require further polypectomy over a 5-year period. Furthermore, patients with Samter’s triad have more aggressive disease and require over seven times as many revision endoscopic surgeries as nontriad patients [40, 41].
Surgery for nasal polyposis associated with AEA results in an 80% subjective improvement rate with a 40% chance or more of recurrence of nasal polyps and persistence of nasal symptoms [42]. Mild to marked improvement in quality of life was reported in individuals with AEA following sinus surgery in a Japanese study [39]. McFadden and colleagues also reported improvements in quality of life and pulmonary function tests (PFTs) and a reduction in systemic and topical corticosteroid requirements [41]. Simple polypectomy alone does not seem to be as useful as FESS owing to the excessive amount of polypoid tissue burden in AEA [43–47].

As the frequency of revision functional endoscopic sinus surgery it is higher in patient with aspirin sensitivity and asthma, Palikhe et al. suggest in their paper that endoscopic sinus surgery should be selected for severe chronic sinusitis with multiply nasal polyps and nasal passage obstruction [48]. Despite these findings, evidence suggests that sinonasal symptoms are significantly improved in the postoperative period following functional endoscopic sinus surgery in patients with aspirin-exacerbated respiratory disease, although the benefit of surgery may be short lived. With regard to improvement also of fraction following functional endoscopic sinus surgery, aspirin-exacerbated respiratory disease (AERD) is a significant predictor of a worse outcome in comparison with patients with allergic rhinitis and nasal polyps [49–53]. When aspirin sensitivity is diagnosed, additional effort should be made to educate patients about nonsurgical management options and the long-term postoperative prognosis. Postoperative, aggressive medical management is necessarily to control the mucosal disease in an attempt to prevent or delay polyp recurrence. The gold standard for medical therapy is the use of intranasal corticosteroids. In some cases, with additional indications, oral corticosteroids can be used with limitations. Patients can also use mucolytics and perform nasal saline douches to remove the thick eosinophilic debris from the sinonasal cavities. After surgery for nasal polyps patients usually continue with topical corticosteroids, antihistamine and antileukotriens tablets. Some of them may also require short course of oral steroids [46, 50, 51, 54–56].

### Biological methods

Inactivation or desensitization is a possible biological approach. The term “desensitization” is widely used in the USA, but is somewhat misleading, as it implies the specific suppression of immunological genuine allergies [57]. The treatment is based on the administration of increasing quantities of acetylsalicylic acid. There is no fix scheme. The first dose is usually 5 mg per day. The single doses are then increased up to 100–300 mg, which must be taken once daily on a long term basis. Depending on the procedure and the patients tolerance, this can last from a few days to two weeks [58, 59]. In about 80% of cases, improvement in nasal respiration, sense of smell and freedom from recurrent polyps are retained for two to three years. The effect can last for up two weeks after salicylate has stopped. There are no consequences if a single dose is omitted or forgotten. If there are longer interruptions (as may be necessary before operations), the treatment must be restarted. It is better to perform the initial phase of treatment in hospital, as there a some risk of adverse reactions such as asthma or gastrointestinal symptoms, particularly in the phase of dose increase. This deactivation is only justified and permissible in patients with established salicylate intolerance [60–63].

It has been suggested that aspirin desensitization followed by aspirin therapy should be considered when the symptoms of aspirin – exacerbated respiratory disease persist despite the optimal use of conventional treatments, or when a patient requires treatment with aspirin or non-steroidal anti-inflammatory drugs for an alternative clinical indications [64, 65]. Suitable patients include the following:

- Moderate or severe asthma and/or intractable nasal symptoms that are uncontrolled with topical corticosteroids and leucotriens-modifying drugs.
- Severe extensive, nasal polyps.
- Requirements for daily or frequent courses of systemic corticosteroids to control nasal symptoms and/or asthma.
- Additional medical indications for aspirins such as atherosclerotic cardiovascular disease.
- Medical indication for other COX-1 enzyme inhibiting medications such as arthritic pain refractory to other anti-inflammatory drugs [64, 65].

Topical lysine-aspirin, administered endonasally, has shown encouraging results in the nasal polyposis in aspirin-exacerbated respiratory disease (AERD) management. The effect of intranasal lysine-aspirin administration on resistant nasal polyps of asthmatics, aspirin-intolerant patients, together with routine therapy, was examined in a well-structured but small prospective study [66, 67].

### Conclusions

The nasal polyps associated with Samter’s triad are often very extensive, difficult to treat, with great tendency to recurrence. Their treatment include preservative treatment options like salicylate avoiding, using selective COX-2 inhibitors, antileukotriens preparates, in some cases glico-corticosteroid preparates as well as aspirin desensitization. The second treatment option is surgical treatment, mainly functional endoscopic sinus surgery. According to the significant frequency of this diseases appearance and often its underdiagnosis we postulate that doctors of different specializations – laryngologists, allergologists should be familiar with all symptoms of this diseases like presented in this paper nasal polypos.

### Authors’ contributions/Wkład autorów

According to order.

### Conflict of interest/Konflikt interesu

None declared.
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