Effect of Tonsillectomy on the Efficacy of Sublingual Immunotherapy

Thesis

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Internal Medicine

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Introduction

Specific immunotherapy (SIT) is a method of reducing sensitivity to a given allergen by repeated administration of a gradually increasing dose of that allergen **(Frew, 2008).**

Together with allergen avoidance, allergen-specific immunotherapy is the only available treatment able to affect the natural course of allergy **(Pipet et al., 2009).**

In 1993, the European Academy of Allergy and Clinical Immunology position paper on specific immunotherapy proposed that sublingual immunotherapy (SLIT) might be used as a therapy to be investigated in order to prove its efficacy and safety **(Pajno, 2007).**

Indications to sublingual immunotherapy (SLIT) include allergic rhinoconjunctivitis, asthma, and isolated conjunctivitis. As to severity of the disease, SLIT is indicated in moderate/severe intermittent rhinitis, persistent rhinitis and mild to moderate asthma **(Ortolani et al., 2006).**

The tonsils are lymphoepithelial structures that provide a protective immunological ring at the openings of both digestive and respiratory tracts **(Marta and Anthony, 1999).**

Tonsils play an immunological role through local and humoral immunity:

Local immunity Tonsillar B cells can mature to produce all the five major Ig classes.

Humoral immunity The Th1 and Th2 cytokines and cytokine mRNA are both detectable in tonsillar hypertrophy and recurrent tonsillitis groups. It showed that human palatine tonsil is an active immunological organ containing a wide range of cytokine producing cells **(Weil-Olivier et al., 2006).**

Slow absorption and processing of the locally retained allergen occurs through the local oral immune system **(Panzner et al., 2008).** If an allergen is given in a high dose by the sublingual route, a small proportion of the administered dose is absorbed through the buccal mucosa and taken up by local dendritic cells. These cells then pass to the regional lymph nodes, where they can interact with antigen-specific lymphocytes **(Frew, 2008).**

Aim of The Study

This study aims to detect the immunological effects of SLIT in allergic patients with tonsillectomy in comparison to allergic patients with normal tonsils.

Allergic Rhinitis

Definition:

Allergic rhinitis (AR) is an upper airway disease that's caused by an IgE-mediated inflammatory reaction after allergen exposure **(Bousquet et al., 2008).** Rhinitis is defined as inflammation of the nasal membranes **(Togias, 2000).** Which is characterized by 4 cardinal symptoms of watery rhinorrhea, nasal obstruction, nasal itching and sneezing **(Bousquet et al., 2001).**

Epidemiology:

Allergic rhinitis is common. It is believed to affect up to 40 percent of children and 10 to 30 percent of adults in the United States **(Settipane, 2001).** The prevalence in the industrialized world is increasing, particularly than in urban areas **(Sly, 1999).** It may be less common in other areas of the world **(Lima et al., 2007).**

Impact of allergic rhinitis on the quality of life:

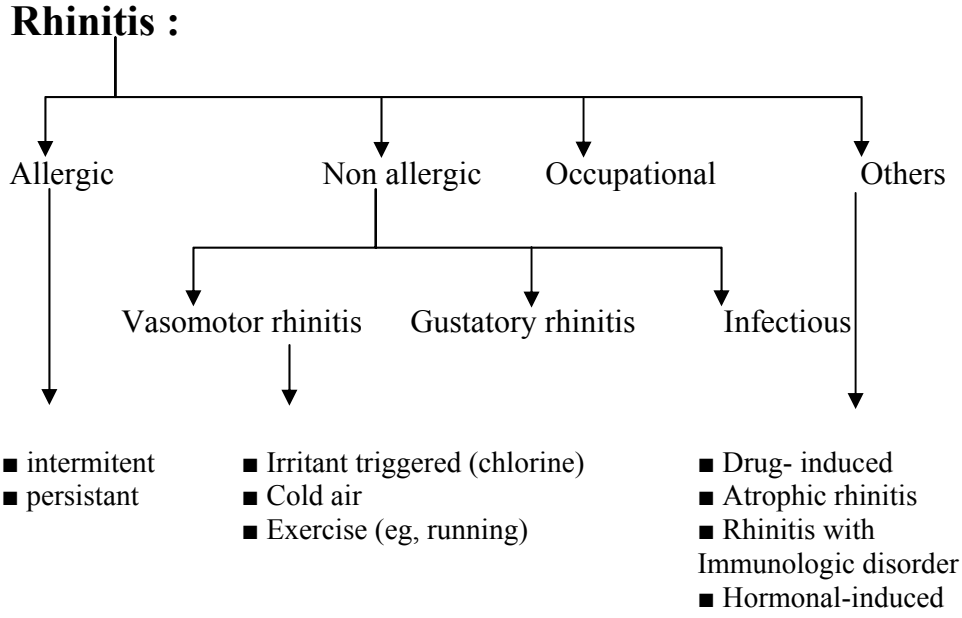
It is important to determine the effect of rhinitis on quality of life (QOL), including symptoms of fatigue, sleep disturbances, learning and attention problems, and absenteeism and presenteeism (present but with impaired function) at work and/or school **(Green et al., 2007).** The psychological ramifications of untreated allergic rhinitis can lead to low self-esteem, shyness, depression, and anxiety **(Berger, 2004).**

Recent findings showed that the sexual QOL is affected by seasonal allergic rhinitis and that appropriate treatment improves the patient's sexual functioning emphasizes that allergic rhinitis is an underappreciated disease with systemic effects **(Kirmaz et al., 2005).** As evidence of the disparities between patients' and physicians' perspectives of allergic

rhinitis, the symptom severity and the reduced work, home, and social functioning, as indicators of QOL, are often underrecognized and inadequately treated by the patient's physician **(Meltzer, 2007).**

Types of allergic rhinitis:

Rhinitis is classified as allergic or nonallergic, but not all types of rhinitis can be easily separated into one of these categories. For example, occupational rhinitis has been classified separately from allergic and nonallergic because it may have components of both allergic and nonallergic rhinitis **(Wallace, 2008).**



(Wallace, 2008).

Fig. (a): Types of rhinitis

I. Allergic rhinitis:

In an attempt to classify allergic rhinitis, an international working group (Allergic Rhinitis and its Impact on Asthma

[ARIA]) **(Bernstein et al., 2008),** has proposed a classification for allergic rhinitis that placed patients into 1 of 4 categories: (1) mild intermittent, (2) mild persistent, (3) moderate/severe intermittent, and (4) moderate/severe persistent **(Bousquet et al., 2006).** This classification system discarded the terms seasonal and perennial, emphasizing that an aeroallergen (e.g, grass pollen) that occurs seasonally in one region may be detected throughout the year in another geographical area. The ARIA definition of mild rhinitis may be a useful comparative reference point for other severity grading schemes, this states that none of the following items is present sleep disturbance, impairment of daily activities, leisure, and/or sport, impairment of school or work and symptoms present but not troublesome **(Bousquet et al., 2001).** This updated parameter supports the concept that more severe rhinitis is defined as more symptoms or interference with QOL, because data show that it may not be possible to separate patients into moderate and severe categories **(Bauchau and Durham, 2005).**

Classification of allergic rhinitis:

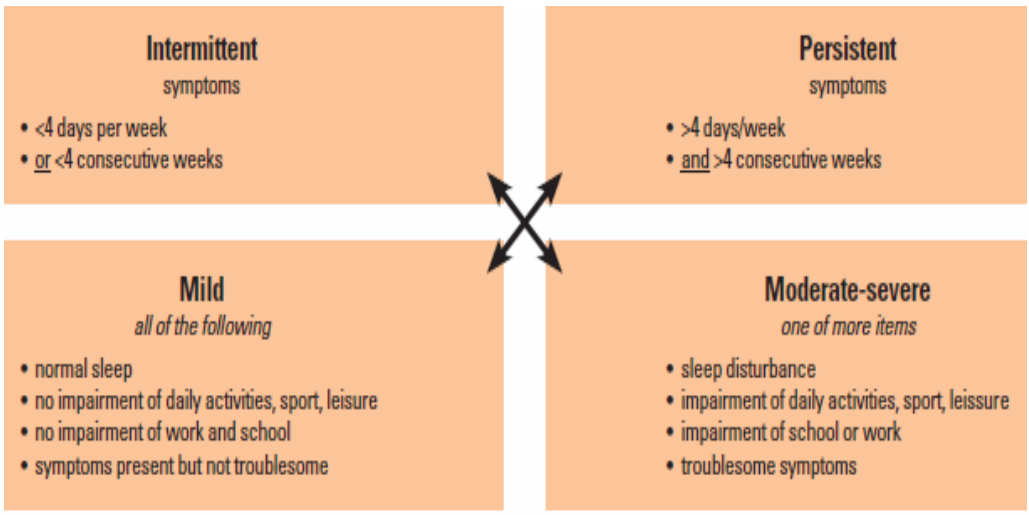


Fig. (b):ARIA classification of allergic rhinitis **(Bousquet et al., 2001).**

Table (a): Types of rhinitis.

II	**Nonallergic rhinitis**
A	**Vasomotor rhinitis**
1	Irritant triggered (e.g, chlorine)
2	Cold air
3	Exercise (e.g, running)
4	Undetermined or poorly defined triggers
B	**Gustatory rhinitis**
C	**Infectious**
1	Acute
2	Chronic
D	**Non allergic rhinitis with eosinophilia syndrome (NARES)**
III	**Occupational rhinitis:** occupational rhinitis has been classified separately from allergic and nonallergic because it may have components of both allergic and nonallergic rhinitis.
A	Caused by protein and chemical allergens, IgE-mediated
B	Caused by chemical respiratory sensitizers, immune mechanism uncertain
C	Work-aggravated rhinitis
IV	**Other rhinitis syndromes**
A	**Hormonally induced**
1	Pregnancy rhinitis
2	Menstrual cycle related
B	**Drug-induced**
1	Rhinitis medicamentosa
2	Oral contraceptives
3	Antihypertensives and cardiovascular agents

Table (a): Cont.

4	Aspirin/NSAIDs (non steroidal anti inflammatory drugs).
5	Other drugs
C	**Atrophic rhinitis**
D	**Rhinitis associated with inflammatory-immunologic disorders**
1	Granulomatous infections
2	Wegener granulomatosis
3	Sarcoidosis
4	Midline granuloma
5	Churg-Strauss
6	Relapsing polychondritis
7	Amyloidosis

(Wallace, 2008)

Pathophysiology of allergic rhinitis:

Pathogenesis of AR:

- **Sensetization to allergen:**

Most causal antigens for AR are inhalant allergens. House dust mite, animal dander and pollens are the principal allergens. Many allergens, including the major house dust-house dust mite allergen, have protease activity that impairs epithelial barrier function and facilitates the penetration of allergens into nasal mucosa **(Wan et al., 1999)** . When sensitized subjects inhale antigens, the antigens pass through the epithelial tight junctions in the nasal mucosa to bind IgE on the surface of mast cells in the epithelial layer of the nasal mucosa, inducing the release of chemical mediators including histamine, prostaglandins, Leukotrienes and kinins. Histamine regulates tight junctions via the coupling of H1 receptors and increases paracellular permeability **(Flynn et al., 2009)**,

professional antigen-presenting cells (APCs) in the nasal mucosa, such as dendritic cells (DC), capture the allergens and provide two distinct signals, the allergen-derived peptide/major histocmpatibility complex (MHC) and co-stimulatory molecules such as CD80 and CD86, to naive T cells **(Kleinjan et al., 2006).**

Early interleukin (IL) -4 and thymic stromal lymphopoietin (TSLP) produced by basophils in response to allergens with protease activity may contribute to Th2 differentiation **(Sokol et al, 2008).** Th2 cells produce IL-4/IL-13 and express CD40L, which promote the class-switching of B cells to immunoglobulin E (IgE) **(Hattori et al., 2006).** Easily andenhance antigen presentation to T cells **(Takano et al., 2005).** Allergen-specific T helper type 2 cells (Th2) are generated in patients with AR, whereas allergen-specific T helper type 1 cells (Th1) are generated in healthy individuals**.**

- **Early and late phase reactions in allergic rhinitis:**

When AR patients are exposed to allergens, allergic reactions develop in 2 different patterns according to time sequence. One is the early reaction, in which sneezing and rhinorrhea develops in 30 minutes and disappears. The other is the late reaction, which shows nasal obstruction approximately 6 hours after exposure to allergens and subsides slowly. The early reaction is the response of mast cells to offending allergens (type I hypersensitivity). Stimulated mast cells induce nasal symptoms by secreting chemical mediators such as histamine, prostaglandins and leukotrienes. In contrast to the early reaction, eosinophil chemotaxis is the main mechanism in the late reaction, which is caused by chemical mediators produced in the early reaction. Several inflammatory cells, eosinophils, mast cells and T cells migrate to nasal mucosa, break up and remodel normal nasal tissue, and these processes result in nasal obstruction which is the main symptom of AR patients **(Min, 2010).**

- **Neurogenic inflammation**

When respiratory epithelium is destroyed and nerve endings are exposed by cytotoxic proteins from eosinophils, sensory nerve fibers are excited by nonspecific stimuli and stimulate both sensory afferent and surrounding efferent fibers, this is called retrograde axonal reflex. This makes the sensory nerve fibers secrete neuropeptides such as substance P and neurokinin A, which induce contraction of smooth muscles, mucous secretion of goblet cells and plasma exudation from capillaries. This process is called neurogenic inflammation **(Min, 2010).**

- **Non-specific hyperresponsiveness**

Non-specific hyperresponsiveness is one of the clinical characteristics of allergic inflammation. Due to eosinophilic infiltration and destruction of nasal mucosa, the mucosa becomes hyperactive to normal stimuli and causes nasal symptoms such as sneezing, rhinorrhea, nasal itching and obstruction. This is a non-immune reaction that is not related to IgE. Hypersensitivity to non-specific stimuli such as tobacco or cold and dry air as well as specific allergens increases in AR patients **(Min, 2010).**

Diagnosis:

The diagnosis of allergic rhinitis is made on clinical grounds based upon the characteristic history (including presence of risk factors), symptoms and signs on physical examination and investigations.

History:

A thorough allergic history remains the best diagnostic tool available. The history will include the patient's chief concerns and symptoms and often includes the pattern,

chronicity, seasonality, and triggers of nasal and related symptoms, family history, current medications, response to previous treatment modalities, presence of coexisting conditions, occupational exposure, and a detailed environmental history. Questions relating symptoms to pollen and animal exposure have been shown to have positive predictive value for diagnosing allergic rhinitis **(Gendo and Larson, 2004).** The presence of consensus risk factors for atopy provides additional support for the diagnosis of allergic disease. This is particularly true for those with a personal or family history of atopic disease, as well as a clear history of animal and pollen triggers of allergic rhinitis symptoms **(Gendo and Larson, 2004).**

Risk factors:

The following are proposed or identified risk factors for allergic rhinitis **(Frew, 2004).**

- Family history of atopy (ie, the genetic predisposition to develop allergic diseases).
- Male sex.
- Birth during the pollen season.
- Firstborn status.
- Early introduction of formula and food.
- Early use of antibiotics.
- Maternal smoking exposure in the first year of life.
- Exposure to indoor allergens, such as animal dander.
- Serum IgE >100 IU/mL before age six.
- Presence of allergen specific IgE.

(Frew, 2004)

Clinical Manifestations

Symptoms:

Allergic rhinitis is associated with a symptom complex characterized by paroxysms of sneezing, rhinorrhea, nasal

obstruction, and itching of the eyes, nose, and palate. It is also frequently associated with postnasal drip, cough, irritability, and fatigue (**Sheikh and Najib, 2009).**

Physical examination:

The physical examination should focus on the nose, but examination of facial features, eyes, ears, oropharynx, neck, lungs, and skin is also important. Look for physical findings that may be consistent with a systemic disease that is associated with rhinitis.

- **General facial features**
    - "Allergic shiners" are dark circles around the eyes and are related to vasodilation or nasal congestion.
    - "Nasal crease" is a horizontal crease across the lower half of the bridge of the nose that is caused by repeated upward rubbing of the tip of the nose by the palm of the hand (ie, the "allergic salute") (**Sheikh and Najib, 2009).**
- **Nose**
    - The nasal examination is best accomplished with a nasal speculum or an otoscope with nasal adapter. In the specialist's office, a rigid or flexible rhinolaryngoscope may be used.
    - The mucosa of the nasal turbinates may be swollen (boggy) and have a pale, bluish-gray color. Some patients may have predominant erythema of the mucosa, which can also be observed with rhinitis medicamentosa, infection, or vasomotor rhinitis. While pale, boggy, blue-gray mucosa is typical for allergic rhinitis,

mucosal examination findings cannot definitively distinguish between allergic and nonallergic causes of rhinitis.

- Assess the character and quantity of nasal mucus. Thin and watery secretions are frequently associated with allergic rhinitis, while thick and purulent secretions are usually associated with sinusitis; however, thicker, purulent, colored mucus can also occur with allergic rhinitis.

- Examine the nasal septum to look for any deviation or septal perforation, which may be present due to chronic rhinitis, granulomatous disease, cocaine abuse, prior surgery, topical decongestant abuse, or, rarely, topical steroid overuse.

- Examine the nasal cavity for other masses such as polyps or tumors. Polyps are firm gray masses that are often attached by a stalk, which may not be visible. After spraying a topical decongestant, polyps do not shrink, while the surrounding nasal mucosa does shrink (**Sheikh and Najib, 2009).**

- **Ears, eyes, and oropharynx**

  - Perform otoscopy to look for tympanic membrane retraction, air-fluid levels, or bubbles. Performing pneumatic otoscopy can be considered to look for abnormal tympanic membrane mobility. These findings can be associated with allergic rhinitis, particularly if eustachian tube dysfunction or secondary otitis media is present **(Hadley, 1999).**

  - Ocular examination may reveal findings of injection and swelling of the palpebral

conjunctivae, with excess tear production. Dennie-Morgan lines (prominent creases below the inferior eyelid) are associated with allergic rhinitis **(Hadley, 1999).**

- The term "cobblestoning" is used to describe streaks of lymphoid tissue on the posterior pharynx, which is commonly observed with allergic rhinitis. Tonsillar hypertrophy can also be observed. Malocclusion (overbite) and a high-arched palate can be observed in patients who breathe from their mouths excessivel **(Vazquez et al., 2006).**

- **Neck**: Look for evidence of lymphadenopathy or thyroid disease.
- **Lungs**: Look for the characteristic findings of asthma.
- **Skin**: Evaluate for possible atopic dermatitis.
- **Other**: Look for any evidence of systemic diseases that may cause rhinitis (e.g, sarcoidosis, hypothyroidism, immunodeficiency, ciliary dyskinesia syndrome, other connective tissue diseases) (**Sheikh and Najib, 2009).**

Investigations:

Primary care clinicians treat the majority of patients with allergic rhinitis, and often initiate therapy empirically, identifying triggers only through the clinical history. This approach is adequate for many patients, although those whose symptoms are severe or refractory to therapy should be referred to an allergy specialist for a more definitive evaluation **(Harmsen et al., 2010).**

The use of diagnostic testing to identify culprit allergens has been associated with improved patient outcome **(Szeinbach et al., 2005).**