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ITALIAN ACADEMY OF RHINOLOGY

The Elder Nose: a narrative review

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Abstract

Over the years senile rhinitis has become a common disease affecting the elder population with a mild yet very bothersome symptom- watery rhinorrhea. Other rhinitis symptoms such as congestion, sneezing, nasal/ocular pruritus, and postnasal drainage can significantly affect the quality of life for older adults. The pathophysiology of senile rhinitis is complex, there are multiple subsets of nociceptive, parasympathetic, and sympathetic nerves that innervate human nasal mucosa along with numerous morphologic alterations, with still much to be discovered about the aging effects these complex mechanisms. One of the objectives of this review is to gain insight to complex structural, physiological and morphological changes that lead to this pathology. The most essential factor in the diagnosis lies in detailed medical history and endoscopic ENT evaluation. Coexisting allergic rhinitis could complicate and delay diagnosis and treatment of senile rhinitis. Intranasal ipratropium bromide has been revealed as a treatment of choice, although this paper presents and explores other valid treatment options which could improve the quality of life of this fragile category of patients. This review aims to report the prevalence and etiopathology, diagnosis and treatment for senile rhinitis.

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Key Words: Senile rhinitis, Ipratropium Bromide, rhinorrhea

Abbreviations:

CRS- chronic rhino sinusitis
NAR- noninfectious rhinitis
AR- allergic rhinitis

IPB- Ipratropium Bromide
INCS- Intranasal corticosteroids
INAH- Intranasal antihistamines

Introduction

Rhinitis is a symptomatic inflammation of the nasal mucosa, causing mild but irritating symptoms such as nasal obstruction, anterior or posterior continuous rhinorrhea, sneezing, or nasal itch. When these constant symptoms are present for at least 1 hour daily for a minimum of 12 weeks per year, the definition chronic rhinitis may be applied. Senile rhinitis affects both genders equally [1]. The pathology becomes (CRS) if the inflammation is extended to the sinonasal cavities and the presence of at least two or more symptoms such as nasal obstruction, facial pain, pressure or fullness, (thick and/or discolored) secretions, and/or decreased sense of smell. The prevalence of CRS is up to 10.9% of the Western population [2]. The severity of the disease may vary from mild to severe and several sub groups can be distinguished based on the etiology: infectious rhinitis, allergic rhinitis; non- allergic noninfectious rhinitis (NAR) and mixed rhinitis. In particular the subgroup of rhinitis without allergy or evident infectious processes will be discussed in this paper. Other subgroups of NAR are: drug-induced rhinitis, hormonal rhinitis including pregnancy-induced rhinitis, non- allergic occupational rhinitis, gustatory rhinitis, and idiopathic rhinitis [3]. Approximate prevalence of NAR worldwide is estimated to be more than 200 million people. Many patients with senile rhinitis may have a concomitant allergic disease that is the reason why the diagnosis of senile rhinitis most often refers to late-onset patients [4]. The manifestation is very variable: intermittent symptoms with perennial allergic rhinitis (AR), or persistent symptoms with seasonal AR The most frequent symptom are bilateral watery nasal secretions without endonasal mucosal and/or anatomic pathology.

Etiopathology

A neurogenic parasympathetic/sympathetic dysregulation is considered the main cause of the symptoms and it has been evidenced that inflammatory cells or type 2 pathways in the nasal mucosa have no influence in the pathogenesis of the senile rhinitis[5]. The neural regulation of the upper airways is quite complex and consists of sensory, parasympathetic, and sympathetic nerves that are in continuous interaction and regulate epithelial, vascular, and glandular processes in the nasal mucosa. The anatomically defined sensory, parasympathetic, and sympathetic neural systems contain heterogeneous populations of nerve fibers often carrying

unique combinations of neuropeptides [6]. Mucous secretion is mainly regulated by the parasympathetic nervous system and acetylcholine is the main parasympathetic neurotransmitter that regulates its secretion, thus rhinorrhea. Parasympathetic neurons may have two populations: larger diameter acetylcholine containing neurons and smaller diameter neurons that release vasoactive intestinal peptide (VIP) and nitric oxide [6].The sympathetic nervous system controls vascular tone with neurotransmitters norepinephrine (short acting) and neuropeptide Y (long acting) in the nasal mucosa and modulate secretions initiated by the parasympathetic system. Adenosine triphosphate is another transmitter in nasal sympathetic neurons. Sensory neuropeptides and nociceptive C-type fibers such as tachykinins, calcitonin gene-related peptide, neurokinin A, and gastrin-releasing peptide of the trigeminal nerve contribute to mast cell degranulation and itch/sneeze reflexes. Parasympathetic and sympathetic sensory neural systems contain heterogeneous populations of nerve fibers that often harbor unique combinations of neuropeptides. The sensory neurons are responsible for transmitting information about the conditions of inhaled air from the epithelium to the brain stem. Acetylcholine stimulates muscarinic M3 and possibly M1 receptors on glands to cause exocytosis so the response is given by efferent axons in the nasal mucosa and the immediate release of the neurotransmitters. In the elder population these complex mechanisms are altered creating an imbalance. Solitary chemosensory cells of the nasal cavity are specialized epithelial chemosensors that respond to irritants through the canonical taste transduction cascade stimulating peptidergic trigeminal nociceptive (or pain) nerve fibers. Activation of these nasal cells can trigger similar local inflammatory responses such as mast cell degranulation and plasma leakage, and this is only by cholinergic neurotransmission and neural activity and not by release of local inflammatory mediators as previously mentioned[7]. The physiological changes in the elder population are also due to anatomic alterations and mucosal atrophy. The body undergoes a gradual loss of water content, atrophy of collagen fibers and loss of elastic fibers in the dermis. These changes result in weakening of the lateral, superior, and inferior nasal cartilages, retraction of the nasal columella, and downward sagging of the nasal tip resulting in increased nasal airflow resistance [8]. On the other hand, mucosal gland degeneration, loss of lymphatic tissue, and decreased nasal blood flow contribute to atrophy and drying of the nasal mucosa and increased viscosity of the mucus.

The Diagnosis

Detailed medical history is essential because during this phase of interaction with the patient a probable diagnosis has to be made. The following tests have the scope of only confirming or denying the physicians suspicion. Therefore, the age of the patient, the duration and frequency of symptoms, the hormonal state, the occupational/environmental exposure to a list of triggers leading to nasal symptoms, and the systemic and nasal medication use should be investigated. Some of the prescription pharmaceuticals frequently and constantly assumed by the elder

population, such as alpha-1 adrenergic antagonists used for benign prostatic hyperplasia, ACE-inhibitors, beta adrenergic inhibitors and phosphodiesterase inhibitors can induce symptoms of rhinitis. The subsequent step includes anterior rhinoscopy checking up for any anatomical deformities, signs of infection or endonasal crust formation. The ENT specialist should proceed with fiber endoscopy and evaluate whole endonasal cavity including the ostiomeatal complex [9]. The nasal endoscopy is crucial in the diagnosis of prolonged courses of rhinitis, and it may reveal the presence of chronic rhino sinusitis with or without nnasal polyps[2]. Nasal cytology may help to distinguish between an inflammatory or neurogenic etiology of symptoms [10]. This diagnostic method represents a useful, inexpensive and easy-to-apply diagnostic procedure to better detail the phenotypic characteristics of rhinitis [11]. It also allows to detect and quantify the cell population within the nasal mucosa at a given time. In order to exclude allergic rhinitis, Prick test or allergen- specific IgE research in blood sample may be obtained, even though it is practically impossible to test against all possible allergens. Clinical relevance of detected sensitization may be confirmed by history and/or allergen provocation test [12]. Other diagnostic tools have been proposed but are not recommended by international consensus or position papers, such as: measurement of total IgE or allergen-specific IgE in nasal secretions, microbiological analysis of the nasal secretions (with the exception of suspect of symptomatic infection), measurement of nasal hyperactivity and allergy provocative testing. CT scan of the sinonasal cavities is not recommended in elder chronic rhinitis patients, especially without any suspect of polyp formation or surgical intention. And lastly, measurement of markers of cerebrospinal fluid leakage (b2- transferrin or b-trace) via a skull base defect are only indicated in unilateral watery rhinorrhea and should be excluded during the first phase of diagnosis- the medical history.

Chronic Rhino sinusitis with and without Nasal Polyps

There are significant differences in CRS prevalence between the elderly and young people. After endoscopic sinus surgery, nasal polyps recurred less often in the elderly, probably due to smaller eosinophilic infiltration which is known to increase the risk of recurrence[13]. Furthermore, this study investigated the segment of patients with allergy which was significantly higher in young people than in the older population, but found no difference in the prevalence of asthma in both populations. Another study confirmed these results, suggesting that the pathogenesis of the CRS in the elderly is different, less linked with allergy and eosinophilic infiltration, but more with nasal polyp formation [14].

Radiological alterations

There are only a few studies of radiological investigations of nasal symptoms. The estimated prevalence of sinus abnormalities on MRI ranges from 25 to 85%. This wide range may be explained with the simple fact that MRI is not an ideal technique for maxillary- facial imaging

because mucus excess seems bigger or more exaggerated leaving CT with coronal and sagittal sections a better technique for evaluation of nasal- paranasal district. An abnormality of the sinuses, which includes not only simple sinusitis but abnormalities such as tumor or fungal infection, was detected in 153 (47.1%) subjects[15]. In a Japanese study on the elder population, 654 (33.8%) subjects had paranasal sinusitis. Also this study found 17% Lund-Mackay (LM) >0 and 7.4% LM score ≥ 4 respectively[16]. Another study investigated the differences of the maxillary sinus in elderly dentate and edentulous patients with a computed tomography (CT). The most frequent alterations were mucosal thickenings and mucous cysts in dentate patients compared to edentate controls, but most of these abnormalities can be considered chronic [17]. Concluding, the majority of radiological findings regarding the nasal district in the elder population is incidental and asymptomatic.

Treatment

The decreased quality of life of untreated/undiagnosed senile rhinitis significantly increases the risk of other concomitant conditions such as obstructive apnea of sleep, fatigue, headache, general malaise, scarce appetite and weakness. Irritant avoidance and smoking stop should be advised to all the patients [18]. Pharmacological management of geriatric patients is never easy because of large assumption of many different pharmaceuticals and interactions are ought to be avoided. Luckily the therapy for CRS is usually local and does not compromise general status of the patient. The treatment of choice is ipratropium bromide that may be associated with intranasal corticosteroids and saline irrigations.

Ipratropium bromide (IPB), an anticholinergic drug, is effective in reducing the severity and duration of the rhinorrhea in senile patients[19]. IPB is a quarternary ammonium derivative of atropine and is only minimally absorbed across biological membranes [20]. IPB was synthesized as a compound that would be less absorbed than atropine, thereby reducing the risk of systemic anticholinergic side-effects (mydriasis, xerosis, tachycardia), and still retaining its therapeutic action [21]. Its onset of action is 15 minutes and maximal effect is reached in 1 hour. IPB has been demonstrated to be highly effective for hypersecretion in idiopathic rhinitis [19], [22], but does not have any influence on other symptoms like nasal blockage or sneezing [21]. In a study that included 233 patients, this molecule, used three times a day has been shown to reduce rhinorrhea by thirty percent along with modest reduction of post nasal drip, sneezing and congestion [23]. It is the most widely experienced anticholinergic with the average follow-up of 4 weeks. Compared to the placebo, anticholinergic treatment significantly reduces the severity of rhinorrhea both in allergic and non -allergic patients [24]. The benefit was less considerable for nasal congestion, retro nasal drip and sneezing. Minor and infrequent episodes of epistaxis in 9.4% of patients and dryness of the nasal mucosa- 5% of patients- have been documented in literature, but these effects were never important enough to interrupt the treatment. No

alterations have been noticed in the nasal cytology after treatment [23]. Other adverse effects reported included irritation of the nasal mucosa, headache and pharyngitis, although the comparison with placebo has detected a significantly greater risk only for the epistaxis [21]. A practice parameter update on rhinitis, published in 2020, suggests that in patients with perennial allergic rhinitis and non-allergic rhinitis who have rhinorrhea as their main nasal symptom be offered intranasal ipratropium with low certainty of evidence for perennial allergic rhinitis and moderate for non- allergic rhinitis [25]. Combined IPB use with intranasal corticosteroid is more effective than the use of individual molecules.

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of plants of the genus Capsicum such as chili peppers. It belongs to a group of chemicals identified as capsaicinoids. Capsaicin produces a burning sensation when a tissue comes into contact with it. This occurs via binding to transient receptor potential vanilloid 1 (TRPV1) receptor, an ion channel-type receptor, which can be stimulated by heat and physical abrasion [26]. The mechanism of action of capsaicin is quite unique. The initial neuronal excitation evoked by the irritant capsaicin is subsequently followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli [26]. It was established that capsaicin can reduce the density of the innervation of the nasal mucosa and the TRPV1-SP signaling pathway, without affecting the integrity and function of nasal epithelial cells or mast cells, and in this way is able to improve the symptoms in 80% of well-selected infectious rhinitis patients[27]. Unfortunately its effectiveness has not been demonstrated in any forms of allergic or non-allergic rhinitis.

Intranasal corticosteroids

Intranasal corticosteroids (INCS) remain the most effective monotherapy for allergic rhinitis meanwhile the association of intranasal ipratropium bromide and intranasal beclomethasone is demonstrated to be more effective than either active agent alone, in reducing the average severity and duration of rhinorrhea in allergic and non-allergic rhinitis [28, 29, 30].
The onset of action is 6-8 hours after the first dose although clinical improvement may not be apparent for a few days and maximal effect may not be apparent until after two weeks. The local side effects of intranasal corticosteroids include epistaxis (5% to 10%), nasal irritation (5% to 10%) dryness, burning and stinging, headache, crusting, nasal septal perforation (< 1%), candida infection of the nose and pharynx.

Nasal saline irrigations

Nasal lavage with saline solution has also been found to be a helpful alone or as an adjuvant therapy in patients with chronic rhinorrhea and rhino sinusitis [31]. It is best performed immediately prior to intranasal corticosteroids or IPB as it may improve mucus clearance;

remove antigen, inflammatory mediators, or biofilm; enhance ciliary beat; and protect the nasal mucosa. Lavages help to reduce postnasal drip, sneezing, and congestion. It has very minor (burning, irritation) –close to none side effects. Unfortunately, there is not an established consensus regarding method of delivery, volume to use, ratio of isotonic to hypertonic, or frequency.

Antihistamines

Second generation oral antihistamines (cetirizine and levocetirizine, fexofenadine, loratadine and desloratadine) can be prescribed for the management of allergic rhinitis symptoms although they have not been adequately studied [25]. First generation antihistamines are not recommended because of the systemic side effects (sedation, performance impairment, dry mouth, constipation, urinary retention, delirium and ocular pressure changes.). Special caution should be taken into account using these agents in fragile elderly patients [32]. Patients who fail oral antihistamine treatment may be successfully treated with intranasal antihistamines (INAH) that have a more rapid onset of action compared to intranasal corticosteroids (INCS) and oral antihistamines, are more effective than oral antihistamines in the control of nasal congestion, and provide a favorable safety profile [25]. Two molecules- azelastine and olopatadine are approved by the FDA for the treatment of seasonal allergic rhinitis[33] [34]. Azelastine is also approved for the treatment of perennial allergic rhinitis and vasomotor rhinitis.

Discussion

Decreased water content of the body, degeneration of glands that secrete mucus and decreased blood flow in the nose require additional humidification of the nasal cavity [35]. Thus saline irrigations should be administrated before IP or ICS. Patient education is critical in managing senile rhinitis, as the elder are difficult to convince to abandon their habits of incorrect nasal irrigations, administrations or addiction to decongestants[36]. Considered the older age of the patients, at each visit, the physician should review all the current therapies to assess for any drug interactions, examine the technique of nasal instillation and provide clearly written treatment plans as memory may be an issue. Future considerations in the research area should involve aging alterations of microbiome and in local microbiome diversity of the patients with CRS and in patients with concomitant allergic disease [37, 38]. Research in the inflammatory pathways involving epithelial cells, including cytokine production or IgE involment should be another branch of consideration as the cellular mechanisms of aging nasal mucosa remain unknown.

Conclusions

Senile nose phenotype usually has very clear characteristics: watery rhinorrhea without other significant rhinitis symptoms. Through a combination of structural and physiological changes and impaired epithelial barrier function, the elderly are more susceptible to ulceration, atrophy and dried nasal mucosa, formation of intranasal crusts, and epistaxis. The elder individuals are eager to seek treatment because of the bothersome watery anterior drip that is often frequent and substantial. In addition to these physical and emotional impacts on patients, there is also an economic burden deriving from the diagnosis and missed/incomplete treatment of rhinitis. IPB is recommended for use in senile rhinitis and is considered a safe and quality-of-life-improving treatment that may be associated with INCS for even better results.

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