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Allergic Rhinitis (J Máspero, Section Editor)

Allergic Rhinitis and Sexual Dysfunction

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Opinion Statement

Sexual dysfunction is perhaps an important co-morbidity of allergic rhinitis and other upper airway diseases in adults; however, its prevalence and importance are underestimated mainly due to lack of assessment by the physician and lack of reporting by the patients. The clue for a successful treatment relies in adequate diagnosis and understanding of the mechanisms involved in the generation of the symptoms.

Introduction

Allergic rhinitis significantly affects a patient´s quality of life, and sexuality and its disorders are important issues of which patients do not talk about easily [1]. Prevalence of sexual dysfunction both in men and women are biased due to lack of reporting such data, mainly because of the patient´s embarrassment, but also because of the physician's poor interrogatory skills. Sexual dysfunction has been scarcely studied in allergic rhinitis patients (Table 1).

Even though its physiopathology is poorly understood, some evidence suggests that the relationship between sexual dysfunction and allergic rhinitis may be bidirectional. The presence of chronic allergic or non-allergic rhinitis, with or without chronic sinusitis and/or polyps affects both quality and structure of sleep resulting in sleeping disorders that could lead to depression, decreasing libido, and organic sexual dysfunction [2]. Additionally, allergic rhinitis might cause directly sexual dysfunction via other mechanisms, mainly systemic inflammation, as discussed later in this text. Conversely, sexual activity can trigger acute symptoms in patients with allergic rhinitis, as has been published before [3].Lastly, drugs used to treat rhinitis can significantly affect sexual life, as the drugs used to treat impotence can affect the clinical course of rhinitis [4].

The following topics will be approached: a) allergic rhinitis triggered by sexual activity, b) rhinitis symptoms worsening caused by drugs used for sexual dysfunction, c) allergic rhinitis as a cause of sexual dysfunction, d) allergic rhinitis as an indirect cause of sexual dysfunction via previous sleep disturbances, and e) sexual dysfunction caused by drugs used for the treatment of allergic rhinitis.

Table 1. Studies about Sexual dysfunction in allergic rhinitis

Author	Year published	Design	Subject/Population	Main results
Monteseirin et al. [3]	2001	Observational cohort	23 AR patients with post-coital rhinitis, 14 men	No repeated symptoms with other exercise performance similar to sexual intercourse
Kirmaz et al [2]	2005	Case-control	43 seasonal ARC, 40 healthy controls	Significant difference in case and control groups and pre-post analysis of case group after a month of Anti-H1 in validated AR and SD questionnaires scores
Benninger et al. [8••]	2009	Case-control survey	701	Significantly worse scores in sexual function, sleep, and fatigue scores in AR vs. controls and non-allergic rhinologic diseases
Benninger et al. [10•]	2010	Retrospective; pre-post observation	130 CRS patients treated with surgery; 38.1% allergic (NOS)	Significant improvement in sexual function and sleep quality scores after surgery
Gunhan et al. [11]	2011	Case-control, prospective pre-post surgical treatment	29 CRSwP, 30 control, 9 month follow-up. No differentiation of AR patients. Objective measures	Significant difference at baseline between case and controls and in the case group after surgery in all measures taken, including sexual function and sleep
Su et al. [9•]	2013	Retrospective observational cohort	Population based. 64,059 men and similar adjusted control	AR showed as independent risk factor for ED onset (HR: 1.37, 95% CI: 1.24-1.52)

AR allergic rhinitis; *ARC* allergic rhinoconjunctivitis; *Anti-H1* H1 antihistamine drugs; *SD* sexual dysfunction; *HR* hazard ratio; *95% CI* 95% confidence interval; *CRS* chronic rhinosinusitis; *CRSwP* chronic rhinosinusitis with polyps; *NOS* no other specification

Allergic rhinitis and erectile dysfunction in different settings

Allergic rhinitis triggered by sexual activity

A post-coital exacerbation of rhinitis, the so-called Honeymoon rhinitis has been described. Monteseirin et al. [3] published in 2001 a small cohort of 23 patients (nine women and 14 men, median age 39.5 years), 10 of whom had allergy to pollens and seasonal rhinitis and the other 13 of whom were sensitized to house dust mites and had persistent rhinitis. All of them had an exacerbation of rhinitis, with sneezing, rhinorrhea, and nasal blockade of 5 to 15 min of duration, immediately starting after sexual intercourse. Patients with seasonal rhinitis only had post-coital symptoms in pollen season. All patients

were challenged with physical activity described as equivalent to sexual activity (like climbing two stair floors) on three different occasions; none triggered rhinitis symptoms in any patient. Latex or seminal fluid hypersensitivity in all women was ruled out. Some patients had late reactions 5 to 8 h after sexual intercourse, similar to the immediate post-coital reactions. The authors propose sexual excitement more than physical activity as the triggering mechanism, through degranulation of mast cells due to a disproportionate high cholinergic tone during sex. Usually during sex sympathetic tone increases causing vasoconstriction and high nasal patency that can last several minutes until normal nasal cycle settles down again, or until a mild parasympathetic rebound with minimal congestion occurs. In post-coital rhinitis subjects, a pathologically high parasympathetic response takes place, which can improve with anticholinergic drugs [5].

Rhinitis symptoms worsening caused by drugs used to treat sexual dysfunction

Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil, tadalafil, and vardenafil have been charged as drug induced rhinitis culprits [4]. They act in the turbinate erectile tissue rich in PDE-5, through a lytic neurogenic action on adrenergic sympathetic system; in neurons containing norepinephrine and Y-neuropeptide, causing congestion and rhinorrhea. Even some cases of epistaxis after using these drugs have been reported. This drugs have an arteriolar and venular dilating effect, mediated by cyclic guanosine-mono-phosphate (cGMP) resulting in rhinitis in 4% of all cases [6, 7].

Allergic rhinitis as a cause of sexual dysfunction

Three studies that statistically linked sexual dysfunction with allergic rhinitis have been published, while other studies included allergic rhinitis patients, but did not separate them from other conditions, including chronic rhinosinusitis and nasal polyposis.

In year 2005 Kirmaz et al. [2] published the first study that looked into association between sexual dysfunction and rhinitis. In this case-control study 43 patients with seasonal allergic rhinoconjunctivitis and 40 healthy control subjects were evaluated (22 to 46 years old), all sexually active. They evaluated rhinoconjunctivitis and sexual dysfunction symptoms with validated questionnaires according gender. They compared both groups and made a pre-post analysis in the rhinoconjunctivitis group before and after desloratadine p.o. 5 mg/day for 30 days. The results showed significantly worse sexual dysfunction score in rhinoconjunctivitis group compared to controls and a significant improvement with antihistamines, with a statistically significant correlation between rhinitis symptoms improvement and score of sexual function.

Benninger et al. [8••] published in 2009 a second observational study about this issue, consisting of a survey of cases and controls. The cohort was made of the sum of several populations: the population of the validation of a questionnaire (the Rhinosinusitis Disability Index, ISDN) plus patients surveyed online, plus prospective patients of their own practice. They combined them and formed three groups: patients with allergic rhinitis (N: 320), normal controls (N: 44) and controls with chronic non-allergic rhinological diseases (N: 337). On the questionnaire they included an item referring to the impact of allergic rhinitis on sexual life. Even though the methodology was questionable, due to

heterogeneity of the population pooled in a single group, a total of 701 patients showed significantly worse scores related to sexual function, sleep quality, and fatigue in allergic rhinitis subjects compared with those without allergy and controls.

Finally a large population-based study in 2013 was published by Su et al [9•] in Taiwan. It was a retrospective risk analysis of a cohort of 64,059 male patients who were first diagnosed with allergic rhinitis, extracted from an official database from nearly one million people enrolled in the local public health system. They compared them with a control group consisting of the same number of patients without rhinitis, adjusted for co-morbidities, age, and confounders, with a total follow-up of 9 years. They sought for the onset of sexual dysfunction and associated conditions and allergic rhinitis. A significantly higher frequency of erectile dysfunction in the allergic rhinitis group (1.32%) versus the control group (0.95%) was found. Allergic rhinitis proved to be an independent risk factor that increases the risk of erectile dysfunction by 37% [hazard ratio (HR): 1.37, 95% confidence interval (95%CI): 1.24-1.52]. They also found a relationship between the severity of rhinitis and frequency of erectile dysfunction.

Patients with ≥12, 6-11, and ≤6 annual consults to the clinic for allergic rhinitis had a HR of 2.41, 1.63, and 1.36, respectively, for erectile dysfunction, compared to controls. Patients with medication use (nasal corticosteroids and H_1-antihistamines, calculated by sales records and prescription) >4 weeks compared with those of <4 weeks per year had a higher risk of developing erectile dysfunction (HR: 1.18, 95%CI: 1.01-1.39). Publication pitfalls consisted of only including male patients and measuring severity of allergic rhinitis in a questionable way; even though all available data were retrospective, this is the largest risk study published so far. The effect of allergic rhinitis treatment in erectile dysfunction doesn´t seem to have been investigated in this study (as it was an epidemiological study), thus this association seems more related to severity of allergic rhinitis and not the treatment itself.

Some other studies of non-rhinologic allergic diseases associated with sexual dysfunction have been published, including asthma and atopic dermatitis. These studies might have included patients with allergic rhinitis. Though not addressing them explicitly, conclusions could be generalizable.

Benninger et al. [10•] published in 2010 a study evaluating the effect of sinus surgery in 113 patients diagnosed with chronic rhinosinusitis. They administered the ISDN questionnaire to the patients (as they did in the former study previously described) before and at least 9 months after endoscopic sinus surgery. It was a retrospective pre-post observational study. Although patients with allergic rhinitis were not analyzed as a particular group, 38.1% of all patients had some "allergy", 42.5% had asthma, and 13.3% the chronic rhinosinusitis, asthma, and aspirin exacerbated respiratory disease (AERD). A significant improvement in sexual function and sleep quality scores was observed after surgery.

Another study published in 2011 in Turkey by Gunhan et al. [11] evaluated 29 male patients with nasal polyposis and 30 healthy controls adjusted for risk factors. They performed functional and objective measurements of nasal patency, sexual function, and sleep before and after 6 months of nasal corticosteroids with subsequent functional endoscopic sinus surgery (FESS). They used quality of life, nasal symptoms, and daily sleepiness (Epworth) questionnaires, as well

as polysomnography, rhinomanometry, and measurement of nocturnal penile tumescence. The study had a prospective design comparing polyposis patients with controls (in the preoperative period) and pre-post measurements only in the polyposis group (since controls were not further studied). The prevalence of erectile dysfunction measured subjectively (questionnaires) was 34.5%, 10.3%, and 3.3% in the preoperative polyposis group, postoperative patients, and controls, respectively. The nighttime penile tumescence measurements similarly showed a prevalence of 24%, 6.9%, and 3.3%, respectively. The differences among the mentioned measurements were all statistically significant. They did not differentiate between patients with or without allergic rhinitis and provide no clue to figure it out, but probably there have been a significant number of such patients. Even though this was a small trial, objective measures were used.

Finally, two allergic non-rhinitis diseases have also been associated with erectile dysfunction, both based on observational studies derived from the same Taiwanese population-based cohort study of allergic rhinitis by Su et al. [8••]. In the asthma study, 3466 asthmatic subjects were compared with 13,836 controls, and a significant increase in erectile dysfunction (HR: 1.9, 95% CI: 1.27-2.85) was found [12•]. In another study of 3997 consecutive patients with newly diagnosed erectile dysfunction and 19,985 healthy controls, it was more likely that patients in the first group have a history of atopic dermatitis than those in the control group (OR. 1.6 95% CI 1.42- 1.8) [13].

Physiopathology of sexual dysfunction induced by allergic rhinitis

In addition to the known association between sleep-disordered breathing and sexual dysfunction (as discussed below) additional direct mechanisms of allergic rhinitis in sexual function have been proposed. It was suggested that sexuality itself might be diminished due to particular symptoms of rhinitis such as chronic nasal obstruction, rhinorrhea, and sneezing, which produces hyposmia or anosmia directly impacting personal satisfaction derived from sexual activity, even hindering the simple act of kissing the sexual partner [8••]. Some people might not feel sexually attractive or feel embarrassed by their symptoms, which might lead to avoiding intimate contact. It is also thought that the impact of rhinitis on sleep quality, daytime concentration, and fatigue would impact the sexual desire and seek for intimate contact [2]. The remarkable involvement in daily life activities at work, family, and school might make sexual activity become a completely secondary issue [8••]. As in chronic rhinosinusitis with or without polyposis, and not similar to other rhinological diseases such as septal deviation, where there is not such heavy congestion, runny nose, or alterations of smell, might place the inability to perceive odors as one of the leading responsible factors [7]. In the setting of an acute attack of rhinitis, the presence of nasal blockade or discharge may also decrease the libido in these patients [8••].

Another theory to explain the association between rhinitis and sexual dysfunction is inflammation [14]. Allergic rhinitis is not only a local condition, but the inflammatory process spreads systemically, such as in asthma, COPD (chronic obstructive pulmonary disease), and atopic dermatitis. The

accompanying chronic inflammation of low activity in these diseases has been associated with the development of cardiovascular disease, including erectile dysfunction. Inflammatory mediators and cells involved in allergic rhinitis, such as leukotrienes, IgE, and mast cells, have recently been implicated in the pathogenesis of atherosclerosis processes, a relevant fact in the development of erectile dysfunction [15]. IgE has been found in human atherosclerotic lesions, and in murine models it was found to be necessary to induce the synthesis of adhesion molecules and apoptosis of macrophages within the plaque. Leukotrienes may lead to atherosclerosis through leukocyte chemotaxis, vascular inflammation and increased endothelial permeability, and the subsequent degeneration of the extracellular matrix [16].

The evidence linking allergic rhinitis with cardiovascular disease/systemic inflammation is scarce. Matheson et al. [17] identified allergic rhinitis as a risk factor for incidental stroke in a cohort of 9272 patients. An increase in cardiovascular events in asthmatic patients has also been observed, mainly in women [11]. In the study published by Su et al. [8••] a significant increase in mortality of 197% in patients with allergic rhinitis was found, a result not mentioned nor analyzed in the original publication, but presented a relative risk (RR) of 2.97 (95% CI: 2.7-3.27) and deserves to be studied in depth in future studies [18]. A high level of circulating adhesion molecules ICAM-1 and VCAM-1, both participants in atherogenesis, was found in patients with chronic allergic rhinitis that interestingly have also been found at high levels in patients with erectile dysfunction with no cardiovascular risk factors [8••]. An increase in the production of transforming growth factorβ (TGF-β) has also been found in the polyp stroma and sera of patients with nasal polyposis, as well as in the biopsies from cavernosum bodies of patients with vascular erectile dysfunction, associated with increased collagen fiber deposition and fibrosis [10•].

Nitric oxide has also been implicated in the pathogenesis, although its mechanism is unknown. It is considered to be the main non-adrenergic noncholinergic neurotransmitter involved in penile erection, whose main production site is the mucosa of the paranasal sinuses, and has been found dramatically decreased in nasal polyposis, increasing with polypectomy. The medium half-life of nitric oxide in serum is ephemeral, and the role of this rhinosinusal production and its function in genitals is completely unknown [10•]. On the other hand, allergic patients with asthma with eosinophilic inflammation have an increase in production of local nitric oxide, and their prevalence of erectile dysfunction is higher.

Another proposed mechanism is chronic intermittent hypoxia induced by nasal obstruction during sleep with developing sleep apnea syndrome, which causes functional damage to the autonomic nerves to the genitals [10•].

Allergic rhinitis as an indirect cause of sexual dysfunction via sleep disturbances

Symptoms of allergic rhinitis often worsen during the night due to fall in the level of endogenous corticosteroids and the consequential increase in proinflammatory cytokines, mainly in the early hours of the morning, leading to a disruption of normal sleep. Allergic rhinitis causes sleep disorders, mainly snoring and obstructive sleep apnea (OSAHS). It is worsened by poor adherence to treatment and lack of control triggers, because at night subjects are in contact with bed clothing, which is rich in mites that can increase symptoms in

sensitized patients [19]. In a study of allergic rhinitis, 68% of patients with persistent rhinitis and 48% of patients with seasonal rhinitis reported that their condition interfered with normal sleep [20]. It has been reported that patients with nocturnal symptoms of rhinitis ≥ 5 nights a month have more daytime sleepiness and chronically restless sleep than those who had no such symptoms. A lower quality of sleep was associated with more severe rhinitis. Objectively through simplified measurement methods such as sleep polygraphy, a greater disruption of normal sleep was also showed in allergic rhinitis patients compared with controls [15].

In the presence of nasal or nasopharyngeal obstruction during sleep, chest movements decrease and reflexes disappear, leading to changes in the pulmonary circulation, misbalances in ventilation and perfusion, and decreased arterial partial pressure of O2 with increased partial pressure of CO2, and consequentially production of chronically intermittent hypoxia, generation of free oxygen radicals, and systemic inflammatory reaction, which in turn, cause multiple systemic disorders [21]. It is also associated with fragmented sleep architecture by producing frequent microarousals, apneas, and hypopneas, dramatically impacting daytime productivity (work and /or school) and quality of life by producing permanent sleepiness, depression, decreased libido.

In the previously mentioned study by Gunham et al. [10•] patients with nasal polyposis had an Epworth score of sleepiness and an apnea-hypopnea index measured by polysomnography significantly higher than controls that improved after FESS.

Moreover, it has been observed that young people with sleep deprivation have an increase of pro- and anti-inflammatory circulating factors such as IL-6 [22, 23].

Sexual dysfunction caused by drugs used in allergic rhinitis

There is no published evidence showing an association of medications used to treat allergic rhinitis and sexual dysfunction. In the author's personal experience (unpublished data) there are cases of dyspareunia in women treated with systemic antihistamines associated with decongestants (ephedrine or pseudoephedrine), which completely disappeared with treatment withdrawal.

Conclusions

People with allergic rhinitis are more likely to have sexual dysfunction, perhaps as a minimal expression of increased major cardiovascular disease (stroke, myocardial infarction), mainly young people, generally without cardiovascular risk factors as in other age groups occur. More research is needed in this regard and to consider allergic rhinitis as a possible cardiovascular risk factor in young patients. Intensive treatment of symptoms and causes should be prompted for control of inflammation, and thus not only improve quality of life, as affected in these patients, but also to prevent emergence of future more severe conditions that effectively shorten life expectancy.

The current literature on allergic rhinitis and sexual dysfunction supports the idea presented in this review. Some areas have received more attention than others. For example, much is known and has been published about the association of allergic rhinitis and obstructive sleep disorders and its association with

sexual dysfunction. In contrast, little is known about the concrete possibility that chronic low-level inflammation causes vascular disease and erectile dysfunction, which might be valid for men, but that does not fully explain the increased risk that also occurs in women, which is even less studied. As has been described so far, special effort should be made to continue studying the role of cytokine mediators in the production of sexual dysfunction in patients with allergic rhinitis in order to identify specific targets for therapeutic intervention, and to obtain quality data on the impact of allergic rhinitis therapies in sexual dysfunction.

Compliance with Ethical Standards

Conflict of Interest
Dr. Fernando S. Serrano and Dr. Jorge F. Máspero declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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