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Full-length Article

"Allergic mood" – Depressive and anxiety symptoms in patients with seasonal allergic rhinitis (SAR) and their association to inflammatory, endocrine, and allergic markers

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ABSTRACT

A growing number of studies show an association between seasonal allergic rhinitis (SAR) with depression and anxiety. The underlying mechanisms of a link between SAR and affect, however, are still unclear. The objective of the present study was to investigate depressive symptoms and anxiety in SAR patients and their association to inflammatory and endocrine parameters. SAR patients (n = 41) and non-allergic, healthy controls (n = 42) were assessed during (pollen season) and out of symptomatic periods (non-pollen season). Inflammatory cytokine profile (Interleukin [IL]-2, IL-4, IL-6, IL-8, IL-10, IL-17, IFN-γ, TNF-α), Immunoglobulin-E (IgE), hair cortisol concentrations (HCC), as well as sleep quality were measured. The present data show that during acute allergic inflammation SAR patients experienced a significant increase in Beck Depression Inventory (BDI-) II scores when (a) compared to the asymptomatic period and (b) when compared to the non-allergic controls, while no differences in anxiety were observed. Increased BDI-II scores in SAR patients were significantly associated with levels of IL-6 as well as IL-6/IL-10 and IFN-γ/IL-10 ratios and further, to an early age at manifestation of SAR and poor sleep quality. These findings support a close relationship between acute allergic processes and affective states, with inflammatory cytokines, sleep, and age of manifestation as potentially relevant mediators.

1. Introduction

Allergic rhinitis (AR), commonly known as hay fever, is a chronic inflammatory disease of the upper airways characterized by key symptoms such as sneezing, rhinorrhea, and nasal obstruction. Prevalence rates reach up to 23% in Europe and have been increasing over the last decades, turning AR into one of the most prevalent chronic diseases in Western populations (Asher et al., 2006; Bousquet et al., 2008). Based on the ARIA (Allergic Rhinitis and its Impact on Asthma working group) guidelines, AR is differentiated into "intermittent" or "persistent" AR depending on sensitization to seasonal allergens such as pollen (seasonal allergic rhinitis, SAR) or year-round allergens such as animal dander or house dust mite with mild or moderate-to-severe symptomatology (Bousquet et al., 2008). In SAR, pathophysiology occurs in two phases, termed as early and late phase. In the early phase, the inhalant allergen is processed by dendritic cells in the nasal mucosa. Allergen presentation activates specific B-cells to secrete high amounts of allergen-specific immunoglobulin-E (IgE). IgE molecules bind to high-affinity receptors (FcεRI) on mast cells and basophils leading to the release of preformed mediators such as histamine causing the classical immediate allergic responses. The late phase of SAR is observed 6–10h after allergen exposure and is characterized by the activation and influx of inflammatory cells such as eosinophils, basophils, neutrophils, and monocytes. This late response is initiated and maintained by inflammatory cytokines such as IL-4, IL-5, IL-10 or IL-17 and tumor necrosis factor alpha (TNF-α), released by activated Th2, mast cells, and infiltrating monocytes. Activated eosinophils secrete mediators such as eosinophilic cationic protein (ECP) or major basic protein (MBP),

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leading to damage of the epithelial cells and hyper-reactivity of the nasal mucosa. Secretion of IL-4 by mast cells or IL-5 by activated eosinophils perpetuate allergy by promoting continuous IgE production by B-cells (IL-4) and activation and survival of eosinophils via an autocrine mechanisms (IL-5).

Although often trivialized, AR is associated with significantly reduced quality of life, lower work productivity, and poorer school performance (Colás et al., 2012; Kremer et al., 2002; Léger et al., 2006; Meltzer, 2016). Moreover, recent research repeatedly revealed an association of SAR with affective disorders such as depression or anxiety. For example, epidemiologic studies showed that a diagnosis of major depressive disorder is 1.7 times higher in SAR patients compared to non-allergic subjects (Cuffel et al., 1999; Hurwitz and Morgenstern, 1999). Likewise, SAR patients have been found to exhibited a significantly increased risk for panic attacks (odds ratio = 1.8) (Goodwin, 2002) and anxiety disorders (odds ratio = 1.41) (Cuffel et al., 1999). A recent review by Sansone and Sansone (2011) illustrates the consistency of these observations by showing that 10 of 12 studies on depressive symptoms and 9 of 11 studies on anxiety symptoms support an association between allergic diseases and mood disturbances. However, most of these studies are based on one-item self-reports regarding absence or presence of affective disturbances, and therefore lack accuracy in the evaluation of depressive symptoms or anxiety in SAR patients. Additionally, the pathophysiological mechanisms underlying the higher risk of mood disturbances or even of clinically relevant affective disorders in SAR patients remain elusive.

Psychoneuroimmunological data support a close interaction between immune, endocrine, and central nervous system processes. As previously introduced, SAR involves an inflammatory response characterized by a significant release of cytokines such as IL-4, IL-5 (early phase) and IL-6, IL-10, and TNF-α (late phase). A growing number of studies indicate that inflammatory cytokines can result in so-called sickness behavior that shares features with depression (e.g., loss of appetite, withdrawal, fatigue, and decreased libido) (Dunn et al., 2005). These behavioral changes seem to be linked to the ability of cytokines to cross the blood-brain barrier and to act centrally, for example, on limbic structures and neurotransmitter systems, particularly on the synthesis of serotonin (indoleamine 2,3 dioxygenase [IDO] pathway). The serotonergic system is essential in the regulation of emotions and the pathogenesis of depression (Anisman and Merali, 2003; Thayer and Sternberg, 2010). Beside this neurotransmitter pathway, inflammatory processes may indirectly affect regulatory brain circuits via the hypothalamic-pituitaryadrenal (HPA) axis. The release of inflammatory cytokines results in an activation of the HPA axis with increased glucocorticoid secretion (Rivest, 2010). Glucocorticoids are involved in the regulation of emotions via their impact on hippocampal and other limbic structures. Excessive or chronic exposure of glucocorticoids, however, leads to neuronal damage and changes of glucocorticoid receptor levels in hippocampus, and may, in turn, contribute to emotion dysregulation and depression (Gądek-Michalska et al., 2013). Although the molecular mechanisms are still under exploration, both, increased level of inflammatory cytokines and activation of HPA axis are frequently linked to depression and anxiety (Dantzer et al., 2008; Gądek-Michalska et al., 2013; Rosenblat et al., 2014; Staufenbiel et al., 2013). Finally, sleep dysfunctions should be considered as a modulating factor in the relationship of allergy and depression. Allergic rhinitis impairs sleep primarily via obstruction of the nose and release of immune mediators affecting central sleep regulation (Bender and Leung, 2005; Lunn and Craig, 2011; Thompson et al., 2013). Sleep dysfunctions, in turn, are a core symptom and a major risk factor of depression (Franzen and Buysse, 2008). Therefore, inflammation-related worsening of sleep might contribute to the development of mood problems in SAR patients.

The objective of the present study was to examine the impact of acute allergic inflammation in patients with SAR on depressive and anxiety symptoms. Further, the potential role of inflammatory cytokines and endocrine parameters as well as characteristics of the allergic disease (duration of symptomatic episodes, symptom severity, age at allergy manifestation) and sleep quality was explored. We hypothesized that acute allergic inflammation (e.g., during pollen season) in SAR patients would lead to increased depressive and anxiety symptoms, which are (positively) correlated with inflammatory cytokines, cortisol concentrations, and sleep quality, respectively.

2. Methods

2.1. Patients

A total of 41 SAR patients and 42 healthy, non-allergic controls aged 18–45 years were recruited for the study. Each participant of the study visited the University Allergy Center Dresden for evaluation of inclusion criteria. Skin prick test for common grass, tree, and perennial allergens were used to diagnose SAR. Further, clinical symptoms, atopic comorbidities, and disease history were assessed. As an additional validation of SAR, total IgE levels were measured. All SAR patients reported rhinitis symptoms exclusively during pollen season and had a positive skin prick test for at least one grass or tree pollen and/or elevated total IgE level (>100 IU/ml serum). All patients were off allergy medication (i.e., systemic or topical antihistamines, corticosteroids, or mast cell stabilizers) for at least seven days prior to testing. SAR patients with current or recent immunotherapy or perennial allergies were excluded from the study as well as control subjects with a family history of atopy. General inclusion criteria were age between 18 and 45 years, no diagnosed psychiatric or central nervous system disease, and no use of immunomodulating or otherwise interfering medication. The study has been approved by the local ethics committee, and written informed consent was obtained from all participants prior to inclusion. Participants received 60 Euro for taking part in the study.

2.2. Study design

Using a longitudinal, observational design, SAR patients and non-allergic controls were assessed during pollen season (SAR: acute symptomatic period; February - November 2012; "on-season") and during non-pollen season (SAR: asymptomatic, period; November 2012 - February 2013; "off-season"). On-season visits were scheduled after patients experienced at least two successive weeks of allergic symptoms (rhinorrhea, sneezing, nasal congestion, red or watery eyes). A minimum time interval of three month between the two assessments was defined. Assignment to on- vs. off-season in the control group was semi-randomized with study visits during winter time being automatically classified as off-season to uncover potential allergy-*independent* seasonal variations in the assessed mood parameters (e.g., due to shorter phases of day light during winter). To prevent possible sequence effects, the condition of the first testing was balanced across subjects. The study was embedded in a larger study assessing psychological outcomes of SAR (Trikojat et al., 2015).

2.3. Mood assessment

The *Beck Depression Inventory - II* (BDI-II; Hautzinger et al., 2006) was used to quantify depressive symptoms. On 21 items, patients rated the severity of depressive symptoms on a 0–3 scale