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Association between Anxiety and Depression in Allergic Diseases

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Abstract

The aim of the present work is to determine whether there is an association between anxiety, depression and allergic disorders, or any important prevalence between these associations. From September 2010 to September 2014, 148 subjects (88 women and 60 men) ranging in age between 13 and 76 years were enrolled in this study. All the patients had a diagnosis of allergic disease. The Hamilton and Zung psychometric scales were used for anxiety and depression disorders, respectively. The association, if any, of anxiety and depression with allergy was assessed in patients who came for consultation about allergy disorders and who had not previously received psychopharmacological medication or psychotherapy. The presence of anxiety and depression was interpreted as another factor for the onset of allergic symptoms in addition to the classical ones which, taken as a whole, lead to the diagnosis of the disease. The findings showed a positive association of 96% for anxiety and a positive prevalence of 66% for depression. Our conclusions show a positive association between anxiety and allergy and between depression and allergy. These results would indicate the importance of making a correct diagnosis of anxiety and depression and of treating these disorders in allergic patients. This study was conducted with the contributions of Scientific Psychosomatics and Psychoneuroimmunoendocrinology (PNIE).

Keywords: Anxiety; Depression; Psychosometric scales; Hamilton; Zung; Allergic disorder; Psychoneuroimmunoendocrinology

Introduction

Allergic disease or allergy, also known as atopia, is an inflammatory and immunologic disorder. As such, it presents characteristics of both physiopathological processes when reactions are activated. The condition becomes apparent when responding to certain stimuli. Thus, when a foreign substance, that is, an antigen or allergen enters our body, a special hypersensitivity reaction occurs and inflammation appears in different organs: the skin, upper and lower respiratory tracts, the gastrointestinal system, and areas lined with mucous and serous epithelium, sweating glands, and abundantirrigation and innervations, thus allowing the aggressive, and at the same time, defensive action of this immunologic-inflammatory mechanism to begin working.

There are various kinds of allergens causing allergic reactions: infectious, dietary, and environmental, among others. Chemically, they are protein substances responsible for triggering a special immune reaction of the body against foreign invaders, causing the above-mentioned hypersensitivity reaction. It should be pointed out that in order to suffer from allergic disorders, we must be hereditary competent, that is, have epigenetic inheritance. When the action is provokedchemical mediators are released, from the most rudimentary (lymphocytes cells, immunoglobulin's (IgE, IgM, IgG, IgA, IgAs) to the most sophisticated ones, (prostaglandins, leukotriene, pro-inflammatory andanti-inflammatorycytokines). As already mentioned, this exchange takes place strictly in areas lined with mucous, serous epithelium with abundant irrigation and innervations.

Hypersensitivity reactions may trigger life-threatening episodes, such as anaphylactic reactions especially to drugs (antibiotics, analgesics), and very rarely to certain foods. These episodes are true medical emergencies, but other serious events can also occur when patients develop severe asthma attacks, which require immediate medical attention as well.

Some patients may develop mild allergic conditions which are within the expected parameters for allergic reactions or which do not demand urgent care. These episodes led us to consider the presence of certain factors and underlying mechanisms which had not been considered before. Thus, with the contributions of Psychoneuroimmunoendocrinology (PNIE), a major construct integrating the immune, endocrine, nervous, behavioral and neural systems, new elements started to appear which also added to this mechanism [1-7]. These new factors were emotions, stress, anxiety, anguish, and depression. Currently, scientists speak of multi-causality of allergy since not only antigens or traditional causes trigger its occurrence but also emotions, which are increasingly taken into account.

Based on a modern, multi-causal management of allergic conditions alongside with PNIE, we have started to find positive results for the patients and for healthcare teams. These results have noticeably improved the quality of life of our allergic patients; therefore, the difference between stress, anxiety and depression should be accurately made. Stress is the first reaction our body is exposed to when coping with an aggression of any origin. Anxiety and depression may appear later, when stressful situations cannot

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be overcome and the allergic disease might have started. It should be remembered that anxiety and depression can be either symptoms or nosologic entities with signs and symptoms of their own, and the whole process described aboveshould be interpreted within the context of heterogeneity and biological dynamics. Therefore, our study seeks to explore the link between anxiety and depression with allergy, once the disease has become evident and physical and psychic symptoms are present.

The objectives of the present work are firstly, to demonstrate the positive and non-positive association between anxiety and depression in allergy patients and secondly, to suggest that tables or assessment scales for anxiety and depression as the ones used in this study should be introduced in allergy consultations and extend this initial approach model to other medical and psychological specialties. With these aims in mind, a search of the currentliterature was carried out which revealed that cerebral and immune interactions are considered an essential component in psychiatry and medical co-morbidities, making reference to the cytokines model in order to explain the physiopathology of one of the depression theories [8].

Depression has been characterized as a dysfunction in both the suppression and activation of the immune system. A study conducted by Blume J et al. attempts to highlight investigations on immune-regulatory mechanisms of activation/suppression in depressed patients. It also refers to the contributions of PNIE on depression, a paradigm that promotes innovations in the assistance and treatment of depression and its co- morbidities [9]. Leonard emphasizes the concept of depression as a dysfunction of the immune system; he also refers to stress as occurring together with changes in the hypothalamic-hypophysis adrenal axis and the immune system. Both situationsact as triggering factors for anxiety and depression. There follows an increase of pro inflammatory cytokines and glucocorticoids, which contributes to the changes of behavior occurring in depression. A defect in the serotonergic function is associated with hypercortisolemia and with an increase in pro inflammatory cytokines accompanying depression. These cytokines and glucocorticoids increase chemical changes in the tryptophan, which leads to a decrease in cerebral serotonin synthesis and thus to the formation of neurotoxins such as the glutamate agonist quinolinic acid and contributes to the apoptosis of astrocytes, oligodendroglia and neurons. The importance of the inflammation hypothesis of depression raises the possibility of investigating on a new generation of antidepressant molecules which will help to lessen the central inflammatory effects [10].

The association between depression, anxiety and inflammation has been shown to be bidirectional. Depression enhances inflammation and in turn, inflammation promotes depression. Some stressful situations are more potent than others. Furthermore, it is possible that situations of psychological coping and interpersonal relationships may reduce the impact of stress inflammatory mechanisms, according to the PNIE viewpoint [11]. An observational cohort study investigated the links between alexithymia, coping strategies, anxiety, depression, pulmonary function and the control of asthma patients. Alexithymia was significantly associated with the severity of depression and anxiety symptoms. It was also related to impaired pulmonary function. Furthermore, the coping strategies used to control asthma were negative. These findings support a multidimensional strategy of asthma patients, which include psychoeducational and behavioral interventions, thus reducing maladaptive strategies [12]. Goodwin RD et al. investigated the impact of allergy treatment on the association between depression and anxiety. Their findings provided the first evidence of the relationship between medical diagnosis of allergy and depression and anxiety disorders, suggesting that antiallergic treatments should mitigate the effects of this negative relationship [13].

Atopic dermatitis is frequently associated with prolonged stress (anxiety and depression), PNIE being a valid theoretical pillar to understand the underlying mechanisms of the disease. A thorough knowledge of these factors would improve the perspectives of their psychopharmacologic treatment and also of other mediator agents of the skin inflammatory reaction [14]. Psychiatric comorbidities are reported to be common among adolescents suffering from asthma but little is known about underlying psychological factors. Therefore, comorbidity profiles of anxiety and depression were explored in this group of adolescents. It was concluded that the diagnosis of asthma and poor control of the disease in adolescents are associated with excessive psychiatric comorbidity, anxiety and depression [15].

Findeis S et al. studied the relationship between patients with insect stings and levels of anxiety and depression. The subjects were divided into three groups and each was treated with epinephrine, without epinephrine and with specific intradermic immunotherapy, respectively. The group treated with epinephrine had higher mean anxiety and depression scores compared with the other two groups. The (venom immunotherapy) VIT group had the lowest mean and median scores for both anxiety and depression. It appears that VIT not only decreases the risk of anaphylaxis and death, but also improves quality of life by a reduction of anxiety and depression, especially in female subjects. When comparing non-treated patients with patients treated only with epinephrine, it was found that VIT patients had lower anxiety and depression scores [16].

Trzcinska H et al. analyzed the relationship between control levels of patients with asthma, depression and anxiety. They concluded that the prevalence of depression and its severity is significantly related to the level of bronchial asthma control. No significant correlation was observed between levels of anxiety, anxiety disorders and degree of bronchial asthma control. These authors also proposed that the condition of mental disorders should be analyzed, especially depression and anxiety [17].

The effects of anxiety and psychological stress on patients with allergic rhinitis were analyzed by carrying out skin sensitivity tests. It was observed that patients with allergic rhinitis submitted to skin sensitivity test appeared to be more anxious. It was further suggested that anxiety disturbances should be also investigated, which would provide important additional information for decision- taking [18].

Allergic diseases affect a large population of adults also suffering from depression, which is related to immune inflammatory changes. Sanna L et al. studied the incidence of allergy on depression and concluded that there is a potential contribution of allergic disorders to depression. Furthermore, several works have reported that adults with chronic idiopathic urticaria may potentially show psychiatric co-morbidities, most commonly anxiety and depression; however, very little is found in the literature on children [19] . Hergüner S et al. investigated on this topic and concluded that children also present

psychiatric co-morbidities alongside with chronic urticaria. They also suggested that children with chronic idiopathic urticaria should receive an interdisciplinary approach together with a psychiatric-psychological treatment [20].

It is widely accepted that anxiety and depression are most commonly manifested in patients with asthma and therefore, there is a close link between these disorders and the degree of asthma control. Based on this relationship between the immune system and the hypothalamic- pituitary-adrenal axis, the concept of nervous asthma is remarked by making reference to this close connection [21].

Chronic spontaneous urticaria is another disease frequently associated with anxiety and depression. Half of the patients suffering from this disorder present auto reactive chronic spontaneous urticaria; therefore, the existence of psychiatric co-morbidities was investigated. It was found that depression and anxiety scores were lower in patients with autoreactive chronic spontaneous urticaria than in those with non-reactive urticaria. Reactivity was studied using the autologous serum skin test applied with the prick test. It was concluded that auto reactive chronic spontaneous urticaria is a distinct subgroup with low scores of anxiety and depression psychiatric comorbidity compared with those having non-reactive urticaria [21].

Very frequently patients report on food-related allergies, which are supposedly associated with psychological factors, anxiety and depression. Lillestol K et al. conducted a study to determine anxiety and depression in patients complaining of some food hypersensitivity which was seldom confirmed by provocation tests (8%). A high percentage of these patients had irritable bowel syndrome. It was observed that anxiety and depression are common in patients who complain of some kind of food allergy, with a much stronger predominance of anxiety disorders than of depression [22].

Numerous studies have noted the occurrence of anxiety and depression in subjects with chronic skin diseases. Hence, Ponarovsky B et al. investigated the prevalence of anxiety and depression in patients with these disorders, focusing mainly on allergy. They arrived at the conclusion that anxiety and depression rates were higher in patients suffering from chronic skin allergies [23].

Patients with asthma are prone to develop anxiety and depression. Since these co-morbidities may affect quality of life. Urrutia I et al. carried out a study to assess the impact that anxiety and depression may have on the asthma patient´s life. They concluded that these disorders negatively affect the asthmatic population´s quality of life, raising the possibilities that management of these psychological variables may improve asthma control and quality of life [24,25].

Subjects with chronic itching are known to be very difficult to manage. In a study on this pathology, Cotes MES et al. state that urticarial dermatitis is an under recognized cause of this pruritus and therefore, in the absence of clinical findings in the skin patients suffering from this condition undergo long treatments with glucocorticoids. Dermal lesions may be of various kinds; hence, the authors propose an algorithm for the study and management of patients which involve a wide assessment of other causes of pruritus and of the use of immunosuppressive agents and glucocorticoids for patients with recalcitrant itch [26].

A review study on the psychological characteristics associated to the onset and progress of asthma in children and adolescents found that their characteristics and those of their caregivers seem to substantially contribute to the beginning and course of the disease [27].

As said before,anxiety and depression are prevalent in asthma patients; they are associated with an increased number of exacerbations and of devices required for asthma control. Since psychiatry treatment may help to control this disorder, Amelink, M et al. investigated psychiatric interventions in patients who were prednisone-dependent and in those who were not. The results of their study showed that the prevalence of significant depressive symptoms and anxiety symptoms was higher in subjects with severe, prednisone-dependent asthma than in patients with severe, non-prednisone dependent ormild-moderate asthma [28]. There is strong evidence that asthma is linked to an increased frequency of psychiatric symptoms and mental disorders. Therefore, an investigation was undertaken to assess the frequency of anxiety and depression disorders in an asthmatic population and the association with the severity of symptoms, if any. The findings of this study showed a high comorbidity of anxiety and depression disorders and asthma, irrespective of the severity of the disease [29]. Finally, another relevant finding in the area of immunology-allergy interrelated with PNIE was the positive association between allergic disease and anxiety and a positive trend between allergy and depression [30].

Materials and Methods

The present work was conducted on patients who came for their first consultation about immune-allergological disorders to the Centro de Enfermedades Alérgicas, Psicosomáticas y Stress (Center of Allergic, Psychosomatic and Stress Diseases) in the City of Villa María, Cordoba Province, Argentina, between September 2010 and September 2014. One hundred and forty-eight subjects who gave their consent after having been previously informed of the characteristics and objectives of the research were enrolled. In the case of minors, consent was given by their parents. The diagnosis of depression and anxiety was should be based on clinical interview and the degree of anxiety and depression for each patient was determined according to their answers to the corresponding questionnaires: the Zung Scale ((Self-Rating Depression Scale SDS, Zung, 1965) for depression, and the scale proposed by Hamilton for anxiety. All patients underwent clinical examinations compatible with the diagnosis of allergic disorders, in addition to a hypersensitivity skin test to certify hypersensitivity to environmental antigens. Criteria for inclusion were: male and female patients with no psychopharmacological or allergological medication or psychotherapy. Study variables: age (in years); clinical diagnosis of allergic disease; anxiety levels according to scores by the Hamilton Scale; and level of depression based on the Zung Scale. Statistical analysis showed the absolute and relative frequencies of patients according to gender, type of depression, and presence or absence of anxiety. The links between gender and degree of depression, and gender and presence of anxiety were studied. The association between type of disease and depression or anxiety was studied as well. In all cases the association was determined by the Chi-square test. Using a variance analysis, the mean scores obtained in each item of the Zung questionnaire were compared among the groups formed according to the levels of depression detected.

Table 1: Percentages for each anxiety category regarding the total number of patients in each allergy diagnosis.

Diagnosis of allergy	Anxiety (Hamilton scale)		Total (%)
	Anxiety (%)	No-Anxiety (%)	
Dermatitis	100	0	100
Rhino-sinusitis	100	0	100
Urticaria	97	3	100

Multiple comparisons were based on the Fisher´s LSD post-hoc test. In all cases the level of significance was 0.05.

Results

Sample general characteristics

One hundred and forty-eight patients, 88 women (60%) and 60 men (40%) constituted the sample with a mean age of 42 years± 19 years, (range 13-76 years). The most frequently diagnosed disease was rhino sinusitis (IRR) (45% of the patients) followed by urticarias and dermatitis (28% and 27% respectively). Patients with asthma (4 patients), conjunctivitis (1 patient) and generalized pruritus (2 patients) were also observed, but because of their low frequencies, these patients were not included in this study According to the Hamilton scale, positive anxiety was found in 96% of the patients, that is, a positive association between anxiety and allergic disease.

Association between allergic disease and anxiety

Anxiety was observed in all the patients with a diagnosis of dermatitis or of rhino-sinusitis and in 97% of subjects with urticaria (Table 1). The presence of anxiety was associated with the diagnosis of allergic disease (p=0,007).

Association between allergy and levels of depression according to the zung scale

Regarding the diagnosis of depression in the sample of allergic patients, the results found by the Zung scale showed that the prevalence of depression among the 148 patients was 66%, that is to say, we began to demonstrate the link between allergy and depression.

With respect to gender, depression was statistically higher in women (p=0.0057) than in men: value of 0.76 versus 0.55. No significant differences were found between the ratio of patients with slight depression; however, the ratios of cases with moderate and severe depression were statistically higher in women (p=0,038 and p=0,044) respectively. Table 2 shows the absolute and relative frequencies by row for each gender, and the score obtained according to the Zung scale.

In all the patients IRR, dermatitis, giant urticaria and urticaria were the most frequently diagnosed diseases, both in patients without depression as well as in those with slight, moderate or severe depression, except for urticaria, which was not detected in cases of severe depression. Asthma, conjunctivitis, laryngitis, pruritus, psoriasis and rhinitis were also observed (Table 3).

Table 2: Absolute and relative frequencies by row according to gender and depression degree by the Zung scale.

Gender	Normal	Slight	Moderate	Severe	Total
Female	19 (24%)	26 (32%)	21 (26%)	14 (18%)	80 (100%)
Male	30 (46%)	24 (36%)	8 (12%)	4 (6%)	66 (100%)
Total	49 (34%)	50 (34%)	29 (20%)	18 (12%)	146 (*) (100%)

(*) 2 patients didnot indicate gender

Table 3: Absolute and relative frequencies of patients according to immunologic diagnosis and degree of depression by the Zung scale.

Immunological Diagnosis	Degree of depression				
	Normal	Slight	Moderate	Severe	Total
IRR	17	12	10	7	46
Dermatitis	14	10	9	4	37
Giant urticaria	6	9	6	2	23
Urticaria	5	8	2	0	15
Asthma	2	5	0	1	8
Pruritus	2	1	2	2	7
Psoriasis	3	2	1	1	7
Laryngitis	0	1	0	1	2
Conjunctivitis	0	1	0	0	1
Rhinitis	0	1	0	0	1
Pseudolymphoma	1	0	0	0	1
Total	50	50	30	18	148

In order to evaluate the association between the immunological pathologies with higher frequencies and degree of depression, diagnoses were grouped according to the followingcriterion: in one group patients with IRR, and in other group patients with skin-related diseases (dermatitis, pruritus, psoriasis, urticaria and giant urticaria). No significant association was detected between depression and allergic disease; however, there was a strong prevalence of depression in the allergic patients studied. Fifty of the 148 patients had normal values whereas the remaining 98 did present some degree of depression, that is, a prevalence of 66 %. These results clearly show the association between allergic disease and depression, which is the core of our present work.

When comparing the average scores corresponding to each question of the Zung questionnaire among patients with different degrees of depression, only the means of questions 1, 3 and 20 were significantly different considering the four kinds of depression indicated by Zung. Differences were observed between some kinds of depression but not in all of them. For instance, the average score of the answers to questions 6, 7 and 19 was the same in patients with normal, slight, or moderate degree of depression.There was no difference between average scores in questions 2 and 5; that is, the average answer was the same among patients with different degree of depression.

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Discussion

Allergic diseases are basically inflammatory disorders which react with hypersensitivity processes to antigens of various natures: virus, bacteria, environmental substances involving fungi, house dust mites, pollen, animal epithelia, among others. Allergic diseases occur mainly in the upper and lower respiratory systems, skin, exocrine glands,liver (as a central metabolic factory) with symptoms derived from the inflammatory reaction already described: mucus secretion as a result of the starting up of internal mechanisms with the release of allergic reaction mediators: histamine, leukotrienes, prostanglandins, Interleukin (IL) 1,6, TNF (Tumor Necrosis Factor). These chemical mediators begin to act when environmental antigens, which are proteins, enter the organism. They trigger a series of reactions which cause the classical symptoms of allergic diseases. Furthermore, emotions, stress, anxiety and depression play a major role which, added to the abovementioned factors, would altogether start these mechanisms. This is the reason why the present work highlights the importance of the positive link between anxiety, depression and allergic diseases, emphasizing that anxiety and depression added to the traditional causes of allergic disorders, render our patients more vulnerable to these diseases. Our results show that the use of the Hamilton Scale and the Zung Scale in our study to measure anxiety and depression respectively, lends support to these associations.

By using the Zung scale with the chi square statistical association tests and forming two groups within the most statistically significant allergic diseases we have observed that the association is not statistically significant; nevertheless, given the high prevalence of depression (66%), its relationship with allergies becomes really clear. Yet, the following question stillrequires further analysis: in the presence of a disease, many somatizing patients may start mechanisms of cognitive, behavioral denial which are not translated in the scale ratings, the same as other patients who do not know how to interpret or decode their allergic symptoms or associate them to the presence or absence of the items studied by the Zung scale.

The Results section shows a detailed analysis of the most outstanding points where the patients did show association, and other points which do not add any significant information to our search for findings. However, we are absolutely sure that the Zung and the Hamilton scales are excellent instruments to measure depression and anxiety in our patients when they first come for consultation. This current work also postulates that taking into account the positive association between anxiety, depression and allergy, we should pay attention to diagnostic research indicative of disorders, since their early diagnosis and appropriate management enhance the possibilities of successful treatment results and better quality of life for our patients, into whom our efforts and contributions are ultimately channeled, as shown in this work.

In other words, environmental antigens and medicines, the positive association of anxiety and depression, and hereditary vulnerability to develop allergic diseases, all together result in a final denominator: the presence of allergy with all its typical symptoms. Allergic diseases, which have specific treatment, may affect children as well as adults in all their vital stages. Currently, there are varied and sophisticated pharmacological solutions; however, if we consider the above-mentioned postulates, we should be trained to suspect of, diagnose and manage anxiety and depression co-morbidities. Regarding treatment, a wide range of solutions are available, from psychopharmacological medications (anxiolytics, antidepressants, hypnotics, neuroleptics, among others) to the well- demonstrated use of psychotherapies, whatever theories or schools of thought they may support. When proposing a therapeutic approach based on these postulates, particular attention should be drawn to many patients treated only with traditional medical care and pharmacology, in order to detect whether they are "displacing" their symptoms, that is, if they come to consult about an allergic disorder and, when facing so much anguish or depression, they "displace" their problem to another organ by presenting a new symptom, for example, hypertension. Therefore, when a double simultaneous approach is used, it is crucial to bear in mind the vital role of psychotherapy in the prevention of this displacement to a symptom or organ. We may suggest that the importance of diagnosing anxiety and depression when treating allergic diseases is related to this issue, as mentioned earlier. By suspecting and describing the association between anxiety, depressions and allergic disease we open new paths for the diagnosis and treatment of allergy, thus helping to overcome serious difficulties with regard to the results of current therapies. Furthermore, we should not leave aside the role that sleep plays in allergic disorders, an issue we will study and present in future papers.

Several other investigations regarding the relationship between IL1, Il-6, TNF and allergy remain to be done on the bases of the important association between inflammatory disease and depression, as demonstrated in this work. Finally, it is possible to conclude that allergic disease is only one, co-morbidities have been demonstrated to exist and the PNIE paradigm fully explains the internal and metabolic mechanisms occurring in allergic diseases.

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