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Depression symptoms and quality of life among individuals with Aspirin-Exacerbated Respiratory Disease

Jonathan M. Feldman, PhD[a,b], **Ariel E. Zeigler, MA**[a], **Krista Nelson, MA**[a], **Esperanza Morales-Raveendran, MA**[a], **Teresa Pelletier, BA**[c], **Gigia Roizen Gottlieb, MD**[b], **Zhen Ren, MD, PhD**[d], and **Elina Jerschow, MD, MSc**[b]

[a]Ferkauf Graduate School of Psychology/Yeshiva University, Bronx NY

[b]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx NY

[c]Albert Einstein College of Medicine, Bronx NY

[d]Washington University School of Medicine, St. Louis, MO

Abstract

Objective: Patients with aspirin-exacerbated respiratory disease (AERD) have high disease burden due to the severity of asthma and sinonasal symptoms. There is limited research on the psychological well-being and subjective experiences of patients with AERD. This study examined levels of depression symptoms, asthma-related quality of life, and asthma control among AERD patients.

Methods: Thirty-two adults with AERD and 39 patients without AERD (asthma-only) were recruited from outpatient asthma/allergy clinics. The sample was largely comprised of ethnic minority, inner-city patients who ranged in age from 19–84 years old. Participants completed the Beck Depression Inventory (BDI), the Mini Asthma Quality of Life Questionnaire (Mini AQLQ), a self-report rating of asthma severity, and spirometry testing. Asthma control and severity were determined following national guidelines.

Results: AERD patients reported lower levels of depression symptoms (p =.049), better overall asthma-related quality of life (p <.001), and perceived their asthma to be less severe (p =.01) compared to asthma-only patients. However, clinician ratings of asthma severity were more severe for AERD than asthma-only patients (p =.006). No significant differences were found between the groups on asthma controller medications or oral corticosteroid bursts for asthma.

Conclusions: AERD patients may be resilient given their low levels of depression symptoms and positive views of asthma-related impairment despite higher clinician-rated asthma severity. The adult onset nature of asthma in AERD might be a protective factor on mental health. Future studies should explore mechanisms linking AERD and positive psychological health outcomes and subjective perception of asthma.

Corresponding authors: Jonathan Feldman, Ph.D., Ferkauf Graduate School of Psychology, Rousso Building, 1165 Morris Park Avenue, Bronx, NY 10461, Phone: 646-592-4508, Fax: 718-430-3960, Jonathan.Feldman@einstein.yu.edu, Elina Jerschow, MD, MSc, Montefiore Medical Center, Allergy/Immunology Division, Hutchinson Medical Center, 1250 Waters Place, Tower 2, 12th Floor, Bronx, NY 10461, Phone: 845-556-6683 ext. 30, Fax: 914-721-2992, Elina.Jerschow@einstein.yu.edu.

Keywords

mental health; minority groups; protective factors; resilience; signs and symptoms

Introduction

Aspirin-Exacerbated Respiratory Disease (AERD) is a chronic medical condition and an important phenotype of asthma and sinus disease.[1, 2] AERD is characterized by three main factors which include 1) adult-onset asthma, 2) nasal polyps, and 3) respiratory reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs),[2, 3] also known as the Samter's triad.[4] For patients with AERD, exposure to NSAIDs produces a hypersensitivity reaction, similar to an asthma or rhinitis attack.[5] It is common for certain symptoms such as chronic congestion and nasal polyps to develop years preceding a diagnosis,[6] ultimately leading to the onset of AERD. In addition to the uncomfortable presence of nasal polyps, asthma in patients with AERD typically presents as severe, persistent, and difficult-to-treat.[1, 5] The prevalence of AERD in adults with asthma is approximately 7% overall, although this rate increases to 15% among patients with severe asthma.[7] African Americans appear to be at increased risk for AERD.[8]

AERD treatment focuses on either complete avoidance of aspirin and other NSAIDs or aspirin desensitization followed by long term aspirin treatment.[9] The aspirin desensitization involves physician-monitored administration of aspirin to AERD patients, followed by daily aspirin.[10] This treatment has been shown to produce improvement in AERD symptoms and improve quality of life, including a reduction of nasal polyps, sinus infections, need for sinus surgery, and use of inhaled corticosteroid medication[11–13]. Although the success of the desensitization is noted, this treatment is neither available nor appropriate for every AERD patient.[14] Some individuals with AERD prefer to avoid aspirin or to discontinue aspirin treatment once they have started, as it can lead to other complications including gastrointestinal issues and prove to be ineffective for some.[15] In particular, Black and Latino patients appear to be less responsive to aspirin treatment.[16]

The burden of disease in AERD patients is high due to the severity and recurrent nature of symptoms.[15] AERD has been proposed as a phenotype of severe asthma, with characteristics of the disease informing a higher ranking of severity compared to other subtypes of asthma.[17] The severe course of asthma in AERD is reflected by an increased number of nasal symptoms, sinus infections and overall health care utilization observed in these individuals.[12] Patients with AERD report that chronic nasal symptoms including nasal polyps and hyposmia contribute the most to a decline in quality of life, and the majority report daily frustration and a negative effect on quality of life.[15] However, patients with chronic rhinosinusitis with nasal polyps (CRSwNP) with AERD reported no significant difference on a disease-specific quality of life measure tailored to individuals with nasal disorders (Sinonasal Outcome Test 22) compared to CRSwNP patients without AERD.[18] These results indicate the importance of further understanding the impact of AERD on quality of life.

Sufficient understanding of the potential psychological impact of living with and managing AERD is not clear. However, asthma is clearly linked with an elevated risk for several psychological disorders including depression[19]. Individuals with asthma are more likely to have depressive symptoms in adolescence[20] and adulthood[21], with longitudinal data on adults showing a persistence of depressive disorders across a 10-year follow-up[22]. Urban minority adults with asthma appear to be especially at risk for a depressive disorder[23, 24]. Despite the severe nature of AERD, limited research suggests this group may demonstrate an adaptive response to stress and not be at greater risk for psychological symptoms. A review of patient medical records at an allergy clinic in Turkey showed a prevalence rate of 10.1% for a psychological disorder (defined by an existing, physician-provided diagnosis of depression or panic attacks) in AERD patients.[25] However, this rate was not different from an aspirin-tolerant group of asthma patients. AERD was also not associated with symptoms of depression among patients attending a pulmonary outpatient clinic.[26] Similarly, no differences existed on depression symptoms between patients with versus without AERD in a study of CRSwNP patients.[18]

These limited data show that AERD patients may respond in a manner characterized by resilience, which occurs when a favorable outcome prevails despite the presence of risk.[27] This framework has been used when studying urban, ethnic minority samples of individuals with asthma.[28] Despite having severe asthma as defined by objective measures, AERD patients may feel subjectively less impaired and their psychological health may not be affected.

The goal of the current pilot study was to examine the psychological well-being and subjective experiences of patients with AERD. It was hypothesized that patients with AERD would report lower levels of depression symptoms and better asthma-related quality of life, but worse asthma control (measured by asthma symptoms and pulmonary function) compared to individuals with asthma but without AERD, hereafter called asthma-only participants.

Methods

Participants

Individuals 18 years of age and older who were diagnosed with AERD or asthma only were recruited from outpatient asthma/allergy clinics of inner-city hospitals in the Bronx, New York. Both groups were recruited using the same strategies which included provider referrals, mailings from providers, and flyers at outpatient clinics. Participants were recruited from larger, treatment outcome studies.[16, 29]

Inclusion criteria for both groups were physician-confirmed diagnosis of asthma and fluency in spoken English or Spanish. For the AERD patients, additional criteria were nasal polyps and hypersensitivity to aspirin (i.e., history of at least one asthma attack after ingestion of NSAID). AERD diagnosis was confirmed by a physician-performed aspirin challenge[16], as previously described. Exclusion criteria for both groups were: evidence of severe mental disorder or legal incapacitation; current alcohol or substance abuse and/or dependence; acute

or chronic neurological, kidney, liver, or respiratory disorder other than asthma; and smoking history defined by ≥ 10 pack-years.

Procedures

The study was approved by the (Institution Name Removed for Blinding) Institutional Review Board. Written consent was obtained acknowledging voluntary participation in the study and access to patient medical information. The self-report assessments were conducted by research assistants at the clinic. The assessments were comprised of a brief demographic questionnaire, an assessment of asthma control, oral corticosteroid use, self-reported asthma severity, the Beck Depression Inventory (BDI), and the Mini Asthma Quality of Life Questionnaire (Mini AQLQ). Spirometry was conducted by trained research assistants and reviewed by study physicians to confirm the acceptability and reproducibility of the tests according to American Thoracic Standards[30]. Participants were instructed to withhold asthma inhalers the day of their visit. Participants were reimbursed for their participation. Data reported for the present study were collected during the baseline assessment prior to receiving any treatment. Therefore, data were collected prior to initiation of aspirin desensitization.

Measures

Demographics Questionnaire—The demographics questionnaire was comprised of questions to assess participant ethnicity, age, gender, level of education, marital status, smoking history, age of asthma diagnosis, employment status, insurance status, and family household income. Participants also provided information on other comorbid medical conditions.

Depression Symptoms—Depression symptoms were measured by the Beck Depression Inventory-II.[31] The BDI is one of the most widely used assessments for measuring the severity of depression symptoms and has high internal consistency and construct validity in both English[32] and Spanish.[33] It is comprised of 21 items, which assess both the cognitive and affective characteristics of depression (e.g., hopelessness, guilt, irritability), along with the somatic symptoms (e.g., sleep, appetite). Each individual item is scored on a scale ranging from 0 to 3 with higher scores indicative of increasingly severe depression symptoms. The BDI total score is the sum of all individual responses, indicating the presence of minimal (0–13), mild (14–19), moderate (20–28), or severe (29–63) depression symptoms.[31]

Asthma-related Quality of Life—Participant quality of life was measured by the Mini Asthma Quality of Life Questionnaire (Mini AQLQ). The Mini AQLQ is a 15-item questionnaire used to asses four quality of life domains over the past two weeks: symptoms, activity limitation, emotional function, and environmental stimuli.[34] The measure is available in English and in Spanish and has good reliability and construct validity in both.[34, 35]

Asthma Outcomes—To assess for self-reported asthma severity, individuals from both groups were asked to rate how severe they perceive their asthma to be on a Likert-type scale

ranging from 1 to 5. Higher scores on this measure indicate that an individual perceives their asthma to be increasingly severe. Asthma severity was also rated by study physicians on the basis of the level of medication required to maintain asthma control given that most participants were taking controller medication. For participants who had poorly controlled asthma or were not taking controller medications, asthma symptoms and pulmonary function were further incorporated into the physician ratings of asthma severity in accordance with National Heart Lung and Blood Institute (NHLBI) guidelines.[36] Asthma control was determined by an algorithm on the basis of FEV_1 (% predicted) obtained by spirometry and responses to structured questions, which were consistent with NHLBI guidelines.[36] Individuals were classified into one of three categories (well controlled, not well controlled, and very poorly controlled) based on the frequency of asthma symptoms, nighttime awakenings, use of short-acting β_2-agonist for symptom control, interference with normal activity, and lung function (%FEV_1). Individuals from both groups were asked to report on their history of oral systemic corticosteroid bursts for asthma in the past year and were recorded as none, one, two, or more.

Statistical Analyses

Demographics were analyzed for differences between the AERD group and the asthma-only group by using independent samples *t* tests for continuous variables and χ^2 tests for categorical variables. ANCOVA analyses were conducted to examine between group differences on the BDI and AQLQ. Logistic regression analyses were conducted for categorical variables (asthma control, oral corticosteroids, self-reported asthma severity). Participant age and race/ethnicity were entered into the models above as covariates. Asthma severity was a covariate in the AQLQ, oral corticosteroid, and self-reported asthma severity analyses. Gender was not related to dependent measures in this study and the ratio was similar in both groups; therefore, gender was not treated as a covariate. A square root transformation was applied for the BDI. Cohen's *d* values were computed to examine effect size for continuous measures. A moderate effect is defined as 0.50 to 0.79, and a large effect is ≥ 0.80.[37] Statistical analyses were conducted using IBM SPSS v24 statistical software.[38] P values < 0.05 were considered statistically significant.

Results

Seventy-one adults with asthma participated, with 32 in the AERD group and 39 in the Asthma-only group. The overall sample was comprised of 76% females, ranging in age from 19 to 84 years old, with a mean of 42.5 years (SD = 13.1). Study participants were predominantly Latino (61.4%) and Black (24.3%). The AERD group was older and comprised of more Black participants than the asthma-only group, which had a greater percentage of Latino participants (Table 1). Age and race/ethnicity were treated as covariates in all analyses. AERD participants were more likely to be on inhaled corticosteroid (ICS) medication and had a greater percentage of severe-persistent asthma than asthma-only participants, the majority of which met criteria for moderate-persistent asthma. AERD participants reported a shorter duration of asthma than asthma-only participants, which is consistent with the adult onset nature of AERD. No other differences were found between the two groups on demographics or pulmonary function.

Depression Symptoms

AERD participants (M = 8.88 ± 9.77) reported lower levels of depression symptoms on the BDI than asthma-only participants (M = 15.13 ± 12.29) [F (1, 66) = 11.07, p =.049, d = 0.56]. These levels correspond to normal mood (i.e., absence of any mood disturbance) in the AERD group and mild depression symptoms in the asthma-only group. Depression symptoms were not associated with the duration since asthma diagnosis (r =.17, p =.17).

Asthma-related Quality of Life

The AERD group reported better overall asthma-related quality of life than the asthma-only group (Table 2), after controlling for asthma severity, age, and race/ethnicity [F (1, 64) = 21.65, p <.001]. This finding was consistent across all subscales of the AQLQ: Symptoms [F (1, 64) = 14.28, p <.001], Activity limitation [F (1, 64) = 7.77, p =.007], Emotional function [F (1, 64) = 19.37, p <.001], and Environmental stimuli [F (1, 64) = 14.48, p <.001]. The effect sizes (based on Cohen's d) were large for all of these differences between AERD and asthma-only on the AQLQ. Longer duration of asthma was associated with worse asthma-related quality of life in the entire sample (r = −.26, p =.04), which is consistent with the findings above since asthma-only patients had a longer duration of asthma.

Asthma Outcomes

No between-group differences existed on asthma control (based on symptom report and $\%FEV_1$), as the majority of participants in both groups had very poorly controlled asthma (Table 3). Both groups reported similar levels of oral corticosteroid bursts for asthma exacerbations during the past year. However, AERD patients reported their asthma severity as being milder compared to asthma-only patients. AERD patients were less likely to report moderate asthma severity than mild [OR =.18, 95% CI .05 - .69, p = .01], and less likely to endorse severe than mild [OR =.11, 95% CI .02 - .66, p =.02] compared to asthma-only patients. Perception of milder disease severity in AERD patients was in contrast to the more severe clinician ratings of asthma severity. Self-report of asthma severity was not associated with duration of asthma (r =.17, p =.18)

Discussion

The aim of the current pilot study was to investigate depression symptoms, asthma-related quality of life, and asthma outcomes among individuals with AERD, compared to individuals with a diagnosis of asthma alone. The study revealed three main findings. First, individuals with AERD reported significantly lower levels of depression symptoms compared to individuals with asthma-only. Second, individuals with AERD reported better asthma-related quality of life than asthma-only patients. Third, AERD patients perceived their asthma to be less severe than asthma-only patients, although asthma severity rated by physicians showed the opposite pattern. No differences were found between the two groups on asthma control, and most patients had poorly controlled asthma. These findings are consistent with a pattern in AERD patients of resilience based on psychological health and positive subjective perceptions of asthma, despite high levels of asthma severity and poor asthma symptom control. These positive views and low levels of depression symptoms in

this AERD sample may also be interpreted as resilience given the high rate of psychiatric disorders found in other urban, ethnic minority asthma patients.[23]

Our finding on depression symptoms is consistent with the limited, existing research showing depression symptoms are not elevated in AERD patients.[18, 25, 26] A possible explanation for this finding is the age of onset and diagnosis of AERD as compared to the age of asthma diagnosis in patients without AERD. Receiving a diagnosis of a chronic illness such as asthma during childhood can negatively impact the behavioral adjustment and emotional development of these children.[39, 40] AERD is typically diagnosed in adulthood, when an individual has likely developed a stronger sense of self-efficacy and coping skills attributed with managing a chronic illness.[41] Individuals in the current study with asthma-only reported a longer duration of asthma compared to the AERD group. As a result, it is possible that the older age at which AERD patients are diagnosed may impact the formation of the way they view their asthma and the associated threat to their emotional well-being.

The age of onset and diagnosis may also affect asthma-related quality of life. AERD patients experienced less interference from asthma symptoms, activity limitation, emotional dysfunction, and environmental stimuli as compared to the asthma-only group. This finding may also be related to resilience in AERD and ability to enact self-efficacious strategies when managing a severe disease. Shorter duration of asthma was associated with better asthma-related quality of life. Many patients are diagnosed with asthma alone prior to AERD,[6, 42] so an individual's reaction to an AERD diagnosis may not impact one's life in a significantly different or more severe manner.

It is possible that biological factors may also influence the relationship between AERD and depression symptoms. Patients with AERD have been shown to have high levels of leukotrienes.[43] Leukotriene receptor antagonist (LTRA) and 5-lypoxygenase (5-LO) inhibitors are sometimes used as treatments for AERD patients. Montelukast, a commonly prescribed LTRA medication, may have a possible side effect of increasing psychiatric symptoms including feelings of depression and suicidality.[44] [45] Zileuton, a 5-LO inhibitor, may also have side effects of behavioral disturbance.[46] Beside respiratory tissue, leukotriene receptors are also expressed in the brain [47, 48]. Therefore, it is possible that the lower level of depression symptoms reported in AERD patients may be linked with higher leukotriene levels at baseline, which warrants further research in future studies.

Limitations of this study include the use of a small, clinic-based sample. Between-group differences were present on age, race/ethnicity, asthma duration, asthma severity and use of controller medications. Some of these differences were expected due to the adult onset nature of AERD [2, 3] and greater disease severity previously reported [1, 5], and might reflect underlying characteristics of the disease. Although we controlled for age, race/ethnicity, and asthma severity, future studies should attempt to match AERD and asthma-only patients on these characteristics with a larger sample. The measure of asthma-related quality of life (AQLQ) targets interference from asthma symptoms, although the greatest complaints of AERD patients are hyposmia and the presence of nasal polyps,[15] neither of which are addressed on this questionnaire. Finally, although all participants were treatment

seeking, the AERD patients were enrolled in an aspirin treatment study and findings may not be generalizable to all AERD patients.

Conclusions

To our knowledge, this pilot study is the first to directly measure the level of depressive symptoms and use a validated measure of asthma-related quality of life in an AERD sample in the United States. Despite higher levels of asthma severity, individuals with AERD endorsed subjectively less interference from asthma, which is consistent with their report of lower levels of depression symptoms. These findings may have clinical implications for providers to be aware that the perception of asthma severity and interference from asthma reported by AERD patients may be less severe than guideline-based ratings of asthma control and severity. Additional research is needed to fully understand the impact of a diagnosis of AERD on mental health and quality of life not only in ethnic minority patients, but in White patients as well. These findings overall suggest resilience in AERD patients, whereby the presence of a chronic, difficult-to-treat illness did not appear to impair psychological well-being or subjective views of asthma. If these findings are replicated in larger samples of AERD patients, it will be critical to identify the specific mechanisms involved and target these protective factors in future interventions for asthma and other chronic diseases.

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Table 1.

Participant Characteristics by Group

	AERD (n=32)	Asthma-Only (n=39)	*P* value
Age (y), mean (SD)	46.2 (14.0)	39.5 (11.7)	.03
Gender (%)			.85
Male	25.0	23.1	
Female	75.0	76.9	
Race/ethnicity (%)			.01
Latino	41.9	76.9	
Black/African- American	35.5	15.4	
Other	22.6	7.7	
Language of interview (%)			.30
English	84.4	74.4	
Spanish	15.6	25.6	.30
Marital Status (%)			.11
Married	40.6	23.1	
Not Married	59.4	76.9	
Household Income			.06
< $25,000	34.5	57.9	
≥ $25,000	65.5	42.1	
Insurance (%)			.30
Private	53.1	40.5	
Medicaid	46.9	59.5	
Employment (%)			.30
Employed/Student	71.0	59.0	
Unemployed	29.0	41.0	
Education (%)			.06
Less than HS graduate	12.5	33.3	
HS graduate	25.0	10.3	
At least some college	62.5	56.4	
Smoking duration (pack-years), mean (SD)	1.5 (4.4)	2.1 (4.0)	.60
Comorbid medical disease (%)	46.7	56.4	.42
FEV_1 (% predicted), mean (SD)	82.2 (21.2)	79.8 (20.8)	.63
Asthma duration (y), mean (SD)	13.5 (10.3)	22.7 (14.8)	.007
Taking ICS medication (%)	93.8	66.7	.005
Taking LTRA medication (%)	62.5	41.0	.07
Asthma Severity, Clinician rated (%)			.006
Intermittent/Mild persistent	25.0	25.6	
Moderate-persistent	37.5	66.7	
Severe-persistent	37.5	7.7	

[a]Abbreviations: AERD, aspirin exacerbated respiratory disease; FEV_1, forced expiratory volume in 1 second; HS, high school; ICS, inhaled corticosteroid; LTRA, Leukotriene receptor antagonist

Table 2.

Asthma Related Quality of Life

	AERD	Asthma-Only	*P* value	Cohen's *d*
Overall score	5.4 (1.4)	3.9 (1.4)	<.001	1.10
Symptoms	4.7 (1.8)	3.3 (1.4)	<.001	0.89
Activity limitation	6.0 (1.1)	5.0 (1.5)	.007	0.73
Emotional function	5.1 (1.6)	3.5 (1.7)	<.001	0.98
Environmental stimuli	5.3 (1.7)	3.9 (1.6)	<.001	0.89

[a]Abbreviations: AERD, aspirin exacerbated respiratory disease

[b]Values are expressed as mean (SD)

Table 3.

Asthma Outcomes

	AERD	Asthma-Only	*P* value
Asthma control (%)			0.54
Well controlled	22.6	13.2	
Not well controlled	16.1	23.6	
Very poorly controlled	61.3	63.2	
Oral systemic corticosteroid bursts for asthma, past year (%)			0.91
0	25.8	18.0	
1	25.8	28.2	
2 or more	48.4	53.8	
Asthma severity, self-report (%)			0.01
Mild	51.6	17.9	
Moderate	35.5	56.4	
Severe	12.9	25.7	

[a]Abbreviations: AERD, aspirin exacerbated respiratory disease