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Caregiver's depressive symptoms and asthma control in children from an underserved community

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ABSTRACT

Caregiver's or maternal depression has been associated with increased asthma morbidity in children from prosperous nations, but little is known about this link in low and middle-income countries. Objective: To examine if caregiver's depressive symptoms are associated with poor asthma control and abnormal immune responses in school-aged children. Methods: Case-control study of 87 asthmatic children (aged 4–11 years) attending a primary care clinic in an underserved area of Santiago (Chile). Cases were children with poor asthma control (Child Asthma Control Test [cACT] <20 points) and controls were children with adequate asthma control (cACT ≥20 points). The Beck Depression Inventory-II (BDI) and a locally validated family health vulnerability test (SALUFAM) were used to assess caregivers' depression and family health vulnerability. Serum from participating children was assayed for IFN-γ, IL-4, IL-13, TGF-β, cortisol, and total IgE. Results: The mean (SD) age of study participants was 8.23 (2.15 years), and 55.2% were females. Use of inhaled corticosteroids (ICS), family health vulnerability, and caregiver's depressive symptoms were significantly more common in cases than in controls (65.4% vs. 34.6%, $p = 0.003$; 41.3% vs. 24.8%, $p = 0.07$; and 39.1% vs. 19.5%, $p = 0.04$, respectively). There was no significant difference in the level of any serum biomarkers between groups. In a multivariate analysis, only ICS use was significantly associated with better asthma control (OR = 3.56 [1.34–9.48], $p = 0.01$). Conclusions: Presence of caregiver's depressive symptoms is associated with poor asthma control among children from an underserved community, but this association was no longer significant after accounting for ICS use.

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Introduction

In spite of effective treatments and evidence-based clinical guidelines, a high proportion of children with asthma do not achieve disease control [1]. Asthma control has been associated with several medical and psychosocial factors. Economically disadvantaged and minority children experience differentially high morbidity and mortality from asthma [2–4] Moreover, mental illness in caregivers has been associated with childhood asthma [5]. For example, maternal depression has been associated with an increment of 30% in emergency department visits among children with asthma [6], and poor familial functioning (including communication problems, role assignment issues, and weak bonding) has been associated with poor asthma control in children [7]. A birth cohort study reported a significant positive association between maternal stress and/or depression and wheeze at age one year of the offspring [8]. In addition, low household income has been associated with recurrent wheeze at age 3 years [9]. Our group previously reported that poor familial functioning is associated with higher prevalence of childhood asthma and other health problems [10].

In Chile, a population-based survey estimated the prevalence of current depressive symptoms and depression as 17.2% and 21.1%, respectively. In that survey, both conditions were more common in women and individuals of lower socioeconomic status [11]. Asthma and psychiatric disorders may share common pathways [12], as subjects with depression have higher levels of serum Th2 cytokines (IL-4, IL-5, and IL-13) than healthy controls, suggesting a T-helper cytokine imbalance.

The aim of this study was to examine if caregiver's depressive symptoms are associated with poor asthma control in Chilean school-aged children living in an

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underserved community. We hypothesized that caregiver depression and familial health vulnerability leads to poor asthma control in underserved Chilean children, and that this is explained by abnormal immune responses in these children.

Methods

Participants

From September 2013 to May 2014, school-aged children (4–11 years) who lived in La Pintana (an economically deprived community of the southeast metropolitan area of Santiago [Chile]), and who attended a primary care clinic and had a doctor diagnosis of asthma, were invited to participate in the study along with their caregivers. The study sessions took place at the Juan Pablo II Primary Care Clinic, La Pintana. The study protocol was approved by the Ethics Committee of the Pontificia Universidad Catolica de Chile School of Medicine (#10-025). Parents or guardians of all participating children signed a written informed consent, and participants aged seven years and older also provided written informed assent.

Procedures

During the study visit, the child's caregiver completed questionnaires on the socioeconomic characteristics of the family, depression in the caregivers (Beck Depression Inventory version-II [BDI]) [13], and the health vulnerability of the family (SALUFAM) [14]. Caregivers also completed a questionnaire about asthma in their children (e.g., age of onset of wheeze, diagnoses of asthma and atopic diseases, use of inhaled corticosteroids [ICS], and adherence with ICS [with adequate adherence defined as medication use >70% of the time]). Study participants and their caregivers completed the Child Asthma Control Test (cACT) [15].

Cases were defined as children with uncontrolled asthma (a cACT score ≤19 points), and control subjects were defined as children with controlled asthma (a cACT score ≥20 points). The cACT was used to classify asthma control because of high sensitivity (∼70%) and specificity (∼75%) [15].The Spanish version of the cACT test has been widely used [16].

Measures

In the morning during the visit, a blood sample was collected from participating children and stored at 4°C for 24 hours. This sample was transported to the laboratory, where serum was extracted and frozen at −20°C until assayed. To determine T-helper cytokine levels, IFN-γ (a Th1 cytokine), IL-4 and IL-13 (Th2 cytokines), and TGF-β (a Treg cytokine) were measured in serum samples using Enzyme Linked ImmunoSorbent Assay (ELISA) (R&D Systems®, Minneapolis, MN), according to the manufacturer's protocol. The results were expressed in pg/ml for IFN-γ, IL-4, and IL-13; and in ng/ml for TGF-β. Total IgE (eBiosciences®, San Diego, CA) and serum cortisol were measured using an ELISA assay (R&D Systems®, Minneapolis, MN), according to the manufacturer's instructions. IgE level was expressed as ng/ml, and cortisol level was expressed as ng/ml or %B/B_0 (% sample bound/ maximum binding).

Depressive symptoms in primary caregivers were assessed using the BDI-II questionnaire [13], which was developed as a self-administered 21-item scale to assess the severity of depression. The BDI has been extensively used and translated into Spanish [17]. The range categories for depressive symptoms are none (0–9 points), mild (10–18 points), moderate (19–29 points), and severe (30 points) [18]. Using a cut-off ≥13 points, sensitivity and specificity for depressive symptoms are 100% and 99%, respectively. Using the same cut-off, the positive and negative predictive values of this questionnaire are 0.72 and 1, respectively [19].

Family health vulnerability was assessed using the SALUFAM ("Salud de la Familia") questionnaire [14]. This instrument (locally developed for primary care) measures family support and agreement and allows identification of major and minor health vulnerability in families. The questionnaire consists of 13 items: 8 assess "Agreement" and 5 "Support." The SALUFAM range goes from 0 to 65, and lower scores mean worse family support. By using 3.7 points as a cut-off value, the questionnaire has a sensitivity (defined as the ability to detect 20% most vulnerable families) of 83%, and a specificity (defined as the ability to 80% least vulnerable families) of 68%. This instrument discriminates families with good and poor outcomes for several health conditions, including childhood asthma. Indeed, a high health vulnerability score (≤3.7 points) is significantly associated with 83% increased odds of poor asthma control [14].

Statistical analyses

The sample size required to detect a difference of 20% between children with and without asthma control due to depressive symptoms in their caregivers with power ≥80% is 80 children (40 cases and 40 controls), assuming that the prevalence of caregiver's depressive symptoms is 20% and 40% in children with and without controlled asthma, respectively [7].

A comparison of children with and without controlled asthma was performed using a Fisher's exact test for

categorical variables, a chi-square test for trend for ordinal variables, and a Student's t-test or a Mann-Whitney non-parametric test for continuous variables, as appropriate. Multivariate logistic regression was used for the analysis of asthma control with age and gender (both known to be correlated with asthma) as the dependent variables, and covariates with $p < 0.10$ in the univariate analysis considered as independent variables. Statistical analyses were performed using SPSS® v.17 (IBM, Armonk, NY, USA).

Results

Of the 107 children invited to the study, 87 (81.3%) agreed to participate. Of these 87 participants, 46 (53%) had poor asthma control ("cases"), and 41 (47%) had adequate asthma control ("controls"). Study participants had a mean (SD) age of 8.23 ± 2.15 years, and 48 (55.2%) were female. The mother was the primary caregiver of 66 (76%) of the participating children. Cases and controls were not significantly different with regard to clinical or demographic characteristics (Table 1). Similarly, there were no differences between cases and controls with regard to parental asthma, age of asthma onset, rhinitis, dermatitis, or adherence with ICS therapy. However, cases were significantly more likely to report ICS use than controls (Table 1). Children whose caregivers had depressive symptoms were more likely to use ICS than those whose caregivers had no depressive symptoms (76% vs. 54.1%, $p < 0.05$).

Caregiver's depressive symptoms and familial health vulnerability were significantly more prevalent in cases than in controls (Table 1 and Figure 1A). Moreover, there was a significant but weak inverse correlation between caregiver's depressive symptoms and the asthma control test score in the child (r = −0.254 [−0.445 to −0.039], $p = 0.017$) (Figure 1b). We next evaluated if asthma control correlated with serum Th1, Th2, and Treg cytokines. There was no significant difference in any cytokine (TGF-beta, IFN-gamma, IL-4, and IL-13) level between cases and controls (Table 2). Moreover, there was no significant difference in serum cortisol or total IgE level between cases and controls (Table 2).

In a multivariate analysis adjusting for age, gender, ICS use, caregiver's depressive symptoms, and family's health vulnerability, only ICS was significantly associated with a better asthma control (OR = 3.56, 95% CI = 1.34–9.48, $p = 0.01$) (Table 3).

Table 1. Demographics and psychosocial characteristic between cases and controls.

	Cases (cACT ≤ 19pts) $n = 46$	Controls (cACT ≥ 20pts) $n = 41$	*P*-value
Age	8.17 ± 2.14	8.13 ± 2.19	0.763
Sex (female)	54.3	56.1	0.870
Primary caregiver:			
Mother	80.4	70.7	0.566
Father	2.2	2.4	
Grandmother	10.9	22.0	
Others	6.5	4.9	
Civil status of primary caregiver:			0.298
Married	52.2	48.8	
Divorced	8.7	4.9	
Cohabitant	15.2	22.0	
Single	23.9	17.1	
Widower	0	7.3	
Education of primary caregiver:			0.530
Incomplete elementary school	15.2	9.8	
Elementary school	34.8	43.9	
High school	39.1	26.8	
Technician	8.7	17.1	
University	2.2	2.4	
Annual family income (US$):			0.737
<$3,500	40.0	36.6	
$3,500-$6,850	48.9	56.1	
$6,850-$13,700	11.1	7.3	
Heating at home:			0.949
Gas	52.2	55.0	
Electricity	19.6	17.5	
Firewood	4.3	5.0	
Kerosene	19.6	15.0	
Others	4.3	7.5	
No of members of family	4[4–4]	5[3–7]	0.617
No of brothers	1[1–1]	1[0–2]	0.672
Allergic rhinitis	72.1	75.7	0.717
Atopic dermatitis	50.0	45.5	0.702
Smoking at home	56.5	51.2	0.602
Age of onset of wheezing (months)	18 [12–24]	16 [11–20]	0.698
Age of asthma diagnosis (months)	37[30–45]	32 [25–40]	0.41
Father's asthma	28.1	25.0	0.785
Mother's asthma	38.9	41.2	0.845
Inhaled corticosteroids	65.4	34.6	**0.003**
Adherence to ICS treatment*	52.9	47.1	0.316
Primary caregiver depression**	39.1	19.5	**0.038**
Family health vulnerability¶	41.3	24.8	0.074

Numbers are expressed in %, mean ± SD, or median [IQR].
*Defined as ICS used >70% of the time.
**BDI (Beck Depression Inventory) with score >13 points.
¶SALUFAM with score < 3.7 points cACT = Child Asthma Control Test; ICS: inhaled corticosteroid.

Discussion

Among school-aged children living in an economically deprived community of Santiago (Chile), caregiver's depressive symptoms were significantly associated with poor asthma control in an unadjusted analysis. However, this association became non-statistically significant in a multivariable analysis adjusting for age, gender, and ICS use. Indeed, only ICS use was significantly associated with better control of asthma in this multivariate analysis, emphasizing the importance of ICS in asthma treatment in general, and among children whose caregivers have depressive symptoms in particular.

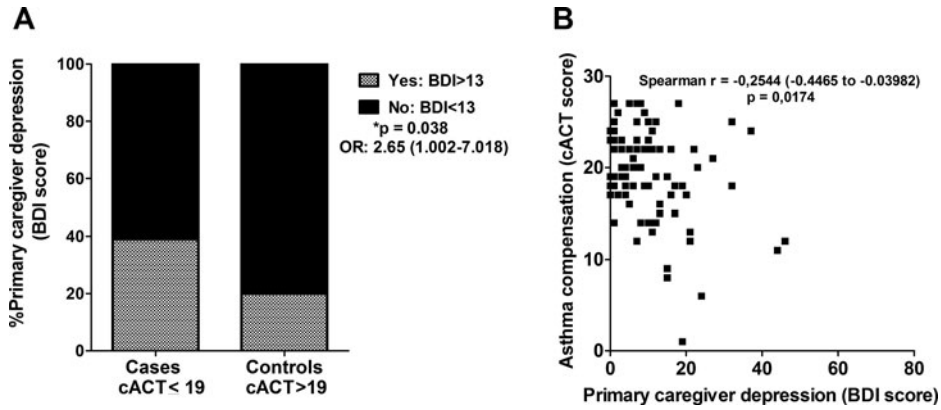

Figure 1. (A) Prevalence of caregiver's depressive symptoms and asthma control test in the child. (B) Correlation between caregiver's depressive symptoms and asthma control test in the child.

Table 2. Biomarkers and cytokines profile between cases and controls.

	Cases (cACT ≤ 19pts) $n = 46$	Controls (cACT ≥ 20pts) $n = 41$	*P*-value
IL-4 (pg/ml)	0 [0–49]	0 [0–110]	0.239
IL-13 (pg/ml)	20.12 [5.72–537.91]	18.67 [6.68–665.64]	0.322
IFN-gamma (pg/ml)	2.50 [0–149.53]	2.78 [0–399.6]	0.99
TGF-beta (ng/ml)	35.53 ± 11.96	38.05 ± 14.18	0.383
Cortisol (ng/ml)	9.32 [2.55–71.21]	7.75 [2.98–51.44]	0.532
Cortisol (%B/B_0)	59.00 ± 15.14	61.01 ± 13.84	0.531
IgE total (ng/ml)	20 [0–565.5]	20.62 [0–457.44]	0.523

Number was expressed as mean ± SD or median [IQR], according to normal or non-normal distribution, respectively.
%B/B_0 = % sample bound/ maximum binding; cACT = Child Asthma Control Test; Ig = immunoglobulin; IL = interleukin, IFN = interferon, TGF = transform growth factor.

Caregivers' mental illness may affect treatment adherence in children [20], but we found no significant difference in adherence with ICS between cases and controls. However, self-reported adherence is often unreliable. Although a prior study [21] found that depressed caregivers of children with asthma had lower confidence in interactions with their providers and were less likely to feel that their needs were met during the visit, we found no difference in the number of visits to the asthma clinic between children whose caregivers did and did not report depressive symptoms (data not shown). A longitudinal study found an association between asthma in children aged 6–7 years with maternal persistent and increasing high depressive symptoms [22]. Although our results may be partly explained by persistent depression among caregivers (dating to the child's early life), this cannot be adequately explored in the current cross-sectional study.

Table 3. Multivariate analysis for asthma control*.

	aOR	95% CI	*P*-value
Inhaled corticosteroids	3.56	1.34–9.48	**0.01**
Female	0.87	0.34–2.26	0.77
Age	0.99	0.98–1.02	0.71
Family health vulnerability	0.55	0.18–1.69	0.30
Primary caregiver depression	0.47	0.14–1.54	0.23

*Adjusted for gender, age, ICS, family health vulnerability, and primary caregiver depression.

Among school-aged children exposed to chronic maternal distress, those with asthma tend to exhibit lower cortisol levels in response to an acute stressor than those without asthma [23]. Cortisol levels were lower in children with asthma who had atopy or increased airway responsiveness [23]. Early exposure to maternal distress may sensitize children to subsequent stress exposure, but chronic activation of the hypothalamic-pituitary axis may lead to protective adaptations, as chronic stress is associated with flat diurnal cortisol patterns [24]. In the present study, there was no difference in basal morning cortisol level between school-aged children with and without controlled asthma.

Much previous research on stress and cytokine responses has focused on acute stressful events, showing relatively consistent effects of such stress on cytokine responses [25]. In contrast to acute stressful events, urban environments characterized by high rates of poverty include chronic exposure to environmental stressors, neighborhood factors, and poor housing conditions. In the current study, we found no differences in serum levels of Th1, Th2, or Treg cytokines between children with and without controlled asthma. Our negative findings may reflect lack of true biologic effects, limited variability of environmental stressors among children living in the same community, or insufficient statistical power. Of note, similar negative results were obtained in one of the largest recent studies among American young mothers from low-income urban areas, where there was no significant association between composite stressor scores or depression score and pro-inflammatory or type 2 cytokine responses.

In that study, there was no significant interaction between stress and allergy or asthma status [26], suggesting that the relationship between stress, depression, and recurrent wheeze is not mediated by allergic sensitization.

In a prospective study of 81 asthmatic children, parental depressive symptoms were unrelated to eosinophil activity (as a marker of allergy) or asthma [27]. However, family dysfunction was associated with changes in eosinophil count and eosinophil cationic protein (ECP) over a 1-year period. Children who experienced high familial dysfunction at the start of the study but experienced low familial dysfunction at the end of the study had lower eosinophil count and ECP when the study ended [27]. We did not evaluate eosinophilia, but total serum IgE was not significantly different between cases and controls.

Our study has several limitations. First, as this was a cross-sectional case-control study, causality cannot be determined. Second, the study focused on a convenience sample of children receiving their primary care at a single center, which limits the generalizability of our findings to other children in Santiago. Third, we had limited statistical power to detect differences in levels of serum cytokines, cortisol, or total serum IgE between cases and control subjects. Fourth, misclassification of asthma control is possible. However, we used the cACT to assess disease control, as recommended by an American Thoracic Society/European Respiratory Society statement [28]. Fifth, we lack data on severe asthma exacerbations (e.g., hospitalizations or use of oral steroids for asthma).

Parental depression may affect asthma control in children through multiple mechanisms, including familial dysfunction [29], increased reporting or awareness of children's symptoms in anxious parents [30], and reverse causation (e.g., worsening of caregivers' depressive symptoms by poor asthma control in their children) [31]. Our findings further suggest that an integrated health care approach to the management of childhood asthma is needed, where the medical (e.g., ICS use), mental, and social health care needs of children and families need to be addressed in primary health care settings.

In conclusion, we found that depression in primary caregivers is associated with uncontrolled asthma in Chilean schoolchildren, but that that association was no longer significant after accounting for ICS use. Large longitudinal studies are needed to further examine mental health disorders and childhood asthma in low- and middle-income countries such as Chile.

Declaration on interest

The authors declared that they have no conflicts of interest relevant to this article to disclose.

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