Respiratory Medicine 133 (2017) 29–35

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Serum folate concentrations, asthma, atopy, and asthma control in Peruvian children

Andrew Nicholson[a], Suzanne L. Pollard[a,b], John J. Lima[c], Karina M. Romero[b,d], Carla Tarazona-Meza[d], Gary Malpartida-Guzmán[d], Edward Mougey[c], Nadia N. Hansel[b], William Checkley[a,b,*], GASP Study Investigators

[a] Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA
[b] Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, USA
[c] Center for Pharmacogenomics and Translational Research, Nemours Children's Health System, Jacksonville, FL, USA
[d] Biomedical Research Unit, A.B. PRISMA, Lima, Peru

ARTICLE INFO

Keywords:
Asthma
Folate
Asthma control
Atopy
Pediatric asthma
Peruvians

ABSTRACT

Background: The relationship between folate status and asthma-related outcomes has not been carefully examined in low- and middle-income countries where folate deficiency is common.
Methods: Ancillary analysis of an unmatched case-control study in which we analyzed serum folate concentrations in 412 children with asthma and 342 controls living in peri-urban communities in Lima, Peru. We examined baseline associations between folate and asthma, atopy, total serum IgE, pulmonary function, and fractional exhaled nitric oxide. We then followed children with asthma longitudinally for 6–9 months and assessed associations between folate and odds of uncontrolled asthma (defined as Asthma Control Test score ≤ 19) and of ≥1 emergency visits during follow-up.
Results: A 10 ng/mL decrease in serum folate was associated with 45% higher adjusted odds of asthma (OR = 1.45, 95% CI 1.05–2.02). The folate-asthma relationship differed by atopic status: a 10 ng/mL decrease in serum folate was associated with a 2.4-fold higher odds of asthma among children without atopy (2.38, 1.20–4.72) and 23% higher odds of asthma in children with atopy (1.23, 0.85–1.80). Among children with asthma, a 10 ng/mL decrease in serum folate was associated with 62% higher odds of uncontrolled asthma (1.62, 1.02–2.56) and 73% higher odds of ≥1 emergency visits during follow-up (1.73, 1.05–2.85).
Conclusions: Serum folate concentrations were inversely associated with asthma, but this effect was stronger in children without atopy. Among children with asthma, lower serum folate concentrations were associated with higher risk of uncontrolled asthma.

1. Introduction

Although the prevalence of asthma in high-income countries has reached a relative plateau, asthma prevalence has continued to increase in many low- and middle-income (LMIC) countries [1,2] with asthma emerging as one of the most prevalent non-communicable diseases [3]. Asthma is the most common chronic disease in childhood, with an estimated 14% of children worldwide experiencing asthma symptoms in the previous year [4]. The underlying mechanisms that help to explain the global asthma epidemic are probably multifactorial and likely affected by multiple genetic and environmental or lifestyle factors, including dietary intake [5].

Folate, and other nutrients acting as methyl donors, could contribute to asthma risk by affecting DNA methylation and, ultimately, gene expression [6,7]. DNA methylation, a type of epigenetic regulation, is a mechanism underlying some gene-environment interactions of complex diseases such as asthma [8]. In particular, changes in DNA methylation can affect the pathogenesis of asthma by increasing or decreasing the expression of disease-susceptibility genes. Although initial findings from mouse models have generated substantial interest regarding the potential role of folate in the pathogenesis of asthma, their relevance to human beings remains unclear. Neither ecological evidence [9] nor evidence from two recent independent reviews [10,11] support a strong effect of periconceptional folate supplementation on increased risk of asthma in humans.

Much of the focus on folate's role in asthma has centered on studies examining the relationship between prenatal use of folate and new-onset asthma. However, few studies have examined whether folate

* Corresponding author. Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, 1800 Orleans Ave, Suite 9121, USA.
E-mail address: wcheckl1@jhmi.edu (W. Checkley).

https://doi.org/10.1016/j.rmed.2017.10.026
Received 7 September 2017; Received in revised form 20 October 2017; Accepted 31 October 2017
Available online 03 November 2017
0954-6111/

status is associated with disease morbidity or disease severity in subjects with established asthma; whether folate status affects asthma control in individuals who already have asthma is also unclear [10,12]. Low folate levels have been shown to be associated with increased risks of wheeze, atopy, severe asthma exacerbations, or an elevated total IgE in cross-sectional studies of children and adults [13–15].

Given evidence from previous studies, we hypothesized that lower serum folate levels are significantly associated with increased odds of asthma, atopy and with decreased asthma control. Given the relative lack of large-scale studies of asthma and folate in the context of LMICs, we sought to examine the relationship between serum folate and asthma outcomes in a cohort of children and adolescents living in two peri-urban communities of Lima, Peru. To test these hypotheses, we examined the relationships among serum folate levels and asthma status, atopy, and asthma control; in addition, we explored the associations between serum folate and pulmonary function measures (spirometry), markers of allergy (IgE, atopy), and markers of inflammation (FeNO).

2. Methods

2.1. Study population and setting

The study population was composed of children and adolescents 9–19 years of age living in the two communities, Pampas de San Juan de Miraflores and Villa El Salvador, located approximately 25 km south of central Lima, Peru. Pampas de San Juan and Villa El Salvador have grown rapidly over the last two decades both economically and in population size; a higher proportion of inhabitants in Pampas was born in the highlands as compared to Villa, and a lower proportion is native to Lima. The two communities also differ in age structure and socioeconomic status (SES); Pampas is less urbanized, has a slightly younger population, and has an overall lower SES. We chose to carry out this study in two communities to increase our recruitment pool of asthma cases. A study conducted in 2010 by our research group in 725 adolescents 13–15 years of age living in Pampas determined that 22% of participants had lifetime wheeze, 12% had current asthma symptoms, and 13% had a physician diagnosis of asthma [16]. This current study was approved by the Institutional Review Boards at the Johns Hopkins University School of Medicine, Baltimore, USA, and A.B. PRISMA in Lima, Peru.

2.2. Study design

This is an ancillary analysis of an unmatched case-control study conducted to determine the role of ambient air pollution on asthma control. For the parent study, Genetics of Asthma Susceptibility to Pollution (GASP), we enrolled children 9–19 years of age living in either of the two study communities. We excluded children with a recorded history of any of the following: ocular, abdominal, or thoracic surgery in the past 3 months, history of hospitalization for cardiac reasons in the past 3 months, a diagnosis of tuberculosis or currently receiving treatment for tuberculosis, a chronic respiratory condition other than asthma, or were pregnant at enrollment. We recruited participants using household census surveys conducted in the study communities. We identified and visited all potential asthma cases aged 9–19 years in the two study communities using birthdate and a positive response to a census question identifying individuals with wheeze or use of asthma medications in the past 12 months, or a lifetime physician diagnosis of asthma. We identified children without asthma using a simple random sample of children aged 9–19 years in our census that responded negatively to all asthma-related census questions. We defined children with asthma as having self- or parental-report of any occurrence of wheezing in the chest or any use of asthma medications in the past year. We confirmed asthma status at enrollment and evaluated asthma severity in accordance with NAEPP-3 guidelines [17]. We defined children without asthma as having no occurrence of self- or parentally-reported wheeze symptoms consistent with asthma in the past year and no use of asthma medications in the past year. In total, we had a final enrollment of 258 and 248 children with asthma, and 374 and 297 without asthma, in Pampas and Villa, respectively. The publication of the parent study, GASP, is currently under review. However, two separate ancillary studies from the parent study have already been published [18,19].

2.3. Questionnaires

We administered a baseline questionnaire, which included questions regarding demographic information, socioeconomic status, asthma medication use, history of allergic rhinitis and eczema, and smoking history.

2.4. Clinical measurements

At enrollment, we conducted spirometry in all participants; we used a flow-based portable spirometer (SpiroPro, Jaeger/ERT, Hoechberg, Germany), obtaining at least three acceptable and reproducible spirometry maneuvers for a maximum of eight in accordance ATS/ERS guidelines [20]. We determined predicted values and Z-scores using multi-ethnic reference values derived by the Global Lung Health Initiative [21]. We measured fractional exhaled nitric oxide (FeNO) using the handheld NIOXMINO (Aerocrine, Solna, Sweden). We measured both total serum IgE and specific IgE antibody to mixes of three common allergens (animal, mold, and dust mite) using the ImmunoCAP 250 (ThermoFisher Scientific, Kalamazoo, MI). An IgE level of > 0.1 kU/L indicated a positive IgE antibody response, and a positive response to any of the three mixes indicated atopy.

To assess asthma control, we used a validated questionnaire to measure an Asthma Control Test (ACT) score [22–24]; for children under 12, the childhood ACT was scored from 0 to 27, and for children 12 years and older, the ACT was scored from 0 to 25. An ACT score ≤ 19 is indicative of uncontrolled asthma. We continued to measure ACT scores and health care utilization visits in children with asthma for up to 9 months. We defined a health care utilization visit during 9-month follow-up as an ED visit or hospitalization as a result of the child's asthma.

2.5. Measurement of serum folate levels

We collected one blood sample per participant using standard phlebotomy techniques at baseline. Blood samples were drawn in the morning and done in a fasting state. We then separated and centrifuged samples within 2 h of extraction and stored samples at -80 °C; we safely stored samples by taking precautions to prevent light exposure before processing. We quantified serum folate levels (ng/mL) at the Analytics Laboratory at Nemours Children Health System, Jacksonville, FL using a Folate Accubind ELISA kit (Monobind). We measured serum folate in duplicate and mean serum folate values for each participant were used to increase reliability and to account for repeated measures. Seasonality was defined based on season of blood draw with the two seasons specified as January–April and September–December.

2.6. Biostatistical methods

We used multivariable logistic regression to model the association between folate and asthma status, atopy status, and the odds of one or more emergency visits for asthma during 9-month follow-up. Asthma models were also stratified by atopy. We used multivariable linear regressions to model associations between serum folate levels and the following outcomes: pre-bronchodilator FEV_1 Z-scores, pre-bronchodilator FVC Z-scores, pre-bronchodilator FEV_1/FVC Z-scores, FeNO (log scale), and total serum IgE (log scale). The regression models for asthma