Asthma 17q21 Polymorphism Associates with COVID-19 in Children

Ioulia Gourari[1], Rika Gomi[1], Madeline Young[1], Geancarlo Jordan[1], Madeline Liongson[1], Andrea Heras[1], Linda Gerber[1], Charlene Thomas[1], Kalliope Tsirilakis[1], Jennie Ono[1], Pramod Narula[2], Thomas Ketas[1], John Moore[1], Stefan Worgall[1], and Perdita Permaul[1]

[1]Weill Cornell Medicine
[2]NewYork-Presbyterian Brooklyn Methodist Hospital

March 23, 2022

Asthma 17q21 Polymorphism Associates with COVID-19 in Children

TO THE EDITOR:

Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in children rarely leads to severe disease. This has been particularly surprising for children with asthma - the most common, chronic inflammatory disease in childhood. We sought to determine predictors for COVID-19 illness in children and adolescents, with and without asthma, exposed to SARS-CoV-2 across the epicenter of the ongoing pandemic in New York City (NYC).

Data collected from May 2020 through April 2021 during the early pandemic and prior to vaccine roll-out as part of the ongoing observational **S** ARS-CoV-2 and **P** ediatric **A** sthma in **N** YC (SPAN) urban cohort study of children and adolescents were analyzed. Study participants were recruited during routine New York-Presbyterian/Weill Cornell Medicine outpatient clinic visits across the epicenter of the COVID-19 pandemic including general pediatrics, adolescent, pulmonary, and allergy clinics. The study population included participants aged 2-21 years without asthma and those with physician-diagnosed asthma for at least one year and at least one of the following: current daily preventive asthma medication use, wheezing in the past year, or an unscheduled healthcare visit for asthma in the past year. Parents/legal guardians of enrolled participants gave written informed consent. Written assent was obtained from participants aged 7-17 years. This study was approved by Institutional Review Boards at Weill Cornell Medicine, NewYork-Presbyterian Queens, and NewYork-Presbyterian Brooklyn Methodist Hospital.

A comprehensive survey administered to the parent/legal guardian included questions regarding demographics, clinical information and exposures, specifically as it pertained to COVID-19 illness. Body mass index (BMI) was calculated using the weight data(kg) and dividing it by height(m) squared(kg/m2). Pediatric age and sex-adjusted BMI percentiles were then calculated using the Centers for Disease Control classification category: normal weight (5-84th BMI percentile), overweight ([?]85-94th BMI percentile), and obese ([?]95th BMI percentile). Blood and nasal biospecimens were collected during the participants' outpatient clinic visits.

As variations at the asthma-risk 17q21 locus associated with ORMDL3 expression, in particular the minor allele of single nucleotide polymorphism (SNP) rs7216389, are strongly linked to childhood asthma and viral triggers for wheezing(1, 2), genotyping of this SNP was performed on extracted DNA using QIAamp DNA blood micro/mini kits (QIAGEN) according to manufacturer's instructions. COVID-19 infection was ascertained by positive SARS-CoV-2 specific antibodies. IgG antibodies against SARS-CoV-2 were determined in plasma by ELISA using the SARS-CoV-2 spike protein as antigen as previously described(3).

Descriptive statistics were calculated to characterize the SPAN cohort (Table 1). Primary outcomes of interest included: 1) positive COVID-19 serology test, and 2) symptomatic COVID-19 illness defined as having a positive COVID-19 test *AND* having at least one of the following symptoms - fever, chills, sore throat, cough, body aches, nasal congestion, rhinorrhea, loss of taste, anosmia, shortness of breath, diarrhea, vomiting, rash, and/or COVID toes, or hospitalization. Univariate logistic regression modeling calculated the unadjusted odds ratio (OR) for each of the demographic and clinical factors of interest on both outcomes, independently. A multivariate logistic regression model evaluated the independent effect of ORMDL genotype on developing COVID-19 while controlling for potential confounders such as age, inhaled corticosteroid (ICS) use, race, borough of residence, household SARS-CoV-2 exposure, and BMI. Collinearity between predictors in the models was evaluated prior to the formulation of the final model. Ninety-five percent confidence intervals for all parameters of interest were calculated to assess the precision of the obtained estimates. All p-values were two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Of 186 participants enrolled, 68 (37%) were infected with SARS-CoV-2, and of these, 38 (56%) endorsed symptoms and two (2.9%) were hospitalized. Sixty-nine participants were obese (38%) while 76 (42%) were healthy weight; 34 (50%) of the obese subset were infected, compared to 22(32%) of healthy weight participants (p =0.03) (Table 1). Multivariable logistic regression analysis showed that obesity (p =0.049) and household SARS-CoV-2 exposure (p <0.001) were risk factors for acquiring SARS-CoV-2 infection while the T/T genotype in asthma participants (p =0.029) was associated with decreased infection risk. Increasing age (p =0.029) was the only predictor associated with more symptomatic infection (Table 2).

The primary objective of this analysis was to better understand the demographic and clinical factors associated with COVID-19 illness in the pediatric population during the early pandemic prior to vaccine roll-out, particularly in those with asthma. Most COVID-19 pediatric investigations have been retrospective analyses of hospitalized children; thus, observational cohort studies in non-hospitalized and healthy children are essential to assess prevalence and risk for COVID-19. As such, the SPAN cohort offers unique data and exhibited a high prevalence of SARS-CoV-2 infection in the outpatient setting; almost half were asymptomatic and unaware they had contracted COVID-19. As anticipated, home contact increased the risk for infection. Similar to adult studies, obesity was associated with more symptomatic illness(4) as was increasing age of the child.

Most notably, we identified a novel association of decreased risk for COVID-19 illness to a common childhood asthma-associated 17q21 genotype. Asthma has not been a distinct risk factor for severe(5) COVID-19 disease in children or adults, and the presence of asthma and allergies may even be protective(6). Steroid use, thought to be a factor for this protective effect(7), was not a confounder in our cohort. Thus, 17q21 asthma-risk genotypes may confer a protective effect against SARS-CoV-2 infection, particularly in children with asthma. It has been demonstrated that children with 17q21 asthma-risk genotypes, such as rs7216389, have lower sphingolipid synthesis(1, 8). Recent findings suggest that sphingolipids may play a role in modulating cellular SARS-CoV-2 entry(9). While a larger replication cohort is needed to validate our findings, our study lays the initial groundwork to uncovering a mechanism for why children with asthma are not as vulnerable to the SARS-CoV-2 virus as originally expected. Moreover, future mechanistic studies are needed to understand how asthma-associated alterations in sphingolipid levels might be implicated in COVID-19 pathology.

References:

1. Ono JG, Kim BI, Zhao Y, Christos PJ, Tesfaigzi Y, Worgall TS, et al. Decreased sphingolipid synthesis in children with 17q21 asthma-risk genotypes. J Clin Invest. 2020;130(2):921-6.

2. Calışkan M, Bochkov YA, Kreiner-Møller E, Bønnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med. 2013;368(15):1398-407.

3. Ketas TJ, Chaturbhuj D, Portillo VMC, Francomano E, Golden E, Chandrasekhar S, et al. Antibody Responses to SARS-CoV-2 mRNA Vaccines Are Detectable in Saliva. Pathog Immun. 2021;6(1):116-34.

4. Sattar N, Valabhji J. Obesity as a Risk Factor for Severe COVID-19: Summary of the Best Evidence and Implications for Health Care. Curr Obes Rep. 2021;10(3):282-9.

5. Lim ZJ, Subramaniam A, Ponnapa Reddy M, Blecher G, Kadam U, Afroz A, et al. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-analysis. Am J Respir Crit Care Med. 2021;203(1):54-66.

6. Green I, Merzon E, Vinker S, Golan-Cohen A, Magen E. COVID-19 Susceptibility in Bronchial Asthma. J Allergy Clin Immunol Pract. 2021;9(2):684-92.e1.

7. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021;9(7):763-72.

8. Rago D, Pedersen CT, Huang M, Kelly RS, Gürdeniz G, Brustad N, et al. Characteristics and Mechanisms of a Sphingolipid-associated Childhood Asthma Endotype. Am J Respir Crit Care Med. 2021;203(7):853-63.

9. Törnquist K, Asghar MY, Srinivasan V, Korhonen L, Lindholm D. Sphingolipids as Modulators of SARS-CoV-2 Infection. Front Cell Dev Biol. 2021;9:689854.

Authors:

Ioulia Gourari, MD[1], Rika Gomi, MD, PhD[1], Madeline Young, BS[1], Geancarlo Jordan, BS[1], Madeline Liongson, MPH[1], Andrea Heras, MD[1], Linda M. Gerber, PhD[2], Charlene Thomas, MS[2], Kalliope Tsirilakis, MD[1], Jennie Ono, MD[3], Pramod Narula, MD[4], Thomas Ketas, BA[5], John P. Moore, PhD[5], Stefan Worgall, MD[1,6,7], and Perdita Permaul, MD[1,6]

Institutional Affiliations:

[1]Division of Pediatric Pulmonology, Allergy & Immunology, Weill Cornell Medicine, New York, NY

[2]Department of Population Health Sciences, Weill Cornell Medicine, New York, NY

[3]Department of Pediatrics, Weill Cornell Medicine, New York, NY

[4]Department of Pediatrics, New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY

[5]Department of Microbiology and Immunology, Weill Cornell Medicine, New York, NY

[6]Drukier Institute for Children's Health, Weill Cornell Medicine, New York, NY

[7]Department of Genetic Medicine, Weill Cornell Medicine, New York, NY

Corresponding Author: Perdita Permaul, MD, Division of Pediatric Pulmonology, Allergy and Immunology, Weill Cornell Medicine, 505 East 70th Street, Helmsley Tower #3F, New York, NY 10021 Telephone: 646-962-3410, Fax: 646-962-0246

Email: pep9004@med.cornell.edu

Funding: This research is supported by NIH K23 AI123517 (PP); R01 AI36082 and P01 AI110657 (JPM); and KL2 TR0002385-05 (AH).

This study received support from NewYork-Presbyterian Hospital (NYPH) and Weill Cornell Medical College (WCMC), including the Clinical and Translational Science Center (CTSC) (UL1 TR000457) and Joint Clinical Trials Office (JCTO).

Conflict of Interests: All the authors declare that there are no conflicts of interest.

Key Words: asthma, children, COVID-19, SARS-CoV-2, SNP, body mass index, BMI

Word Count: 965

Hosted file

Tables.docx available at https://authorea.com/users/466690/articles/560917-asthma-17q21-polymorphism-associates-with-covid-19-in-children