Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

represents in healthy newborns, whether it is related to changing pulmonary vascular resistance, changes in intracardiac or extracardiac shunts, fluid shifts, or all of these processes in concert.

With respect to the statistical analyses performed and our sample size, we created our hypothesis regarding differences in BNP trajectory based on our clinical experience and performed exploratory analyses based on this hypothesis. It is our practice to conduct power analyses in the context of negative findings to ensure that we have not encountered false-negative results. In the receiver operating characteristic curve analyses, we identify robust findings in the accuracy of BNP for prediction of clinical outcome during weeks 3 through 5, with cut-off values that maximize the percent correctly classified, and sensitivity and specificity without bias toward either measure. Despite our sample size, the positive findings for these weeks negates the potential for false-negative results. We are overall reassured that our findings are robust to multiple different analytic approaches.

Elyssa Guslits, MD
Martina A. Steurer, MD, MAS
Department of Pediatrics, Critical Care, University of California San Francisco, San Francisco, California

Hythem Nawaytou, MD
Department of Pediatrics, Cardiology, University of California San Francisco, San Francisco, California

Roberta L. Keller, MD
Department of Pediatrics, Neonatology, University of California San Francisco, San Francisco, California

https://doi.org/10.1016/j.jpeds.2020.11.020

The authors declare no conflict of interest.

References

1. Steurer MA, Moon-Grady AJ, Fineman JR, Sun CE, Lusk LA, Wai KC, et al. B-type natriuretic peptide: prognostic marker in congenital diaphragmatic hernia. Pediatr Res 2014;76:549-54.
2. Menon SC, Tani LY, Weng HY, Lally PA, Lally KP, Yoder BA. Clinical characteristics and outcomes of patients with cardiac defects and congenital diaphragmatic hernia. J Pediatr 2013;162:114-9.e2.
3. Hanslik A, Pospisilb U, Salzer-Muhar U, Greber-Platzer S, Male C. Predictors of spontaneous closure of isolated secundum atrial septal defect in children: a longitudinal study. Pediatrics 2006;118:1560-5.
4. Lusk LA, Wai KC, Moon-Grady AJ, Steurer MA, Keller RL. Persistence of pulmonary hypertension by echocardiography predicts short-term outcomes in congenital diaphragmatic hernia. J Pediatr 2015;166:251-6.
5. Skinner JR, Boys RJ, Hunter S, Hey EN. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. Arch Dis Child 1991;66(4 SPEC NO):386-90.
6. Cantinotti M, Storti S, Parri MS, Prontera C, Murzi B, Clerico A. Reference intervals for brain natriuretic peptide in healthy newborns and infants measured with an automated immunoassay platform. Clin Chem Lab Med 2010;48:697-700.

Coronavirus disease 2019, multisystem inflammatory syndrome in children, apolipoprotein E4, and race

To the Editor:

Kaushik et al presented a series of 33 children from New York City hospitals diagnosed with multisystem inflammatory syndrome in children (MIS-C); 81% had antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Similarly, Carter et al, reported on a series of 25 children diagnosed with MIS-C from the United Kingdom; 68% were SARS-CoV-2 seropositive.[2] The children in both groups exhibited a cytokine profile consistent with a robust innate immune response. At the same time, emerging evidence suggests the hypothesis that the apolipoprotein E4 (apoE4) genotype can predict coronavirus disease 2019 (COVID-19) severity in adults.[3,4] Accordingly, we propose the hypothesis that the apoE4 genotype may identify children at increased risk of developing MIS-C from SARS-CoV-2 infection.

Classically, the apoE4 genotype has been associated with cardiovascular disease and Alzheimer's disease[5]; however, it has also been associated with an enhanced in vivo innate immune response.[6] Notably, individuals of African descent may have twice the frequency of the ε4 allele (30%-40%) compared with those of European or Asian descent,[7] and therefore, they may be more likely to exhibit a stronger innate immune response to the SARS-CoV-2 infection.

In the series presented by Carter et al, the children who were SARS-CoV-2 seropositive exhibited more severe disease; 8 of 9 black children compared with 5 of 10 white children in the series were SARS-CoV-2 seropositive.[2] Of 21 patients with a depressed systolic ventricular function in the report by Kaushik et al, 11 were black and 1 white (Table 4).[1] This suggests an overrepresentation of black children diagnosed with MIS-C from severe SARS-CoV-2 infection.

Therefore, as seen with adults, the apoE4 genotype may identify children at a greater risk of severe SARS-CoV-2 infection; and in particular, MIS-C.

Mark R. Goldstein, MD, FACP
NCH Physician Group
Center for Healthy Living
Naples, FL

Gregory A. Poland, MD, MACP, FIDSA, FRCP (London)
Mayo Clinic and Foundation
Rochester, MN

Charles W. Graeber, MD
NCH Healthcare System Internal Medicine Residency
Affiliate of the Mayo Clinic School of Medicine and Science
Naples, FL

https://doi.org/10.1016/j.jpeds.2020.10.072

The authors declare no conflicts of interest.

References

1. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020;224:24-9.
2. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med 2020;26:1701-7.
3. Goldstein MR, Poland GA, Graeber CW. Does apolipoprotein E genotype predict COVID-19 severity? QJM 2020;113:537-8.
4. Kuo CL, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, et al. ApoE E4 genotype predicts severe COVID-19 in the UK Biobank Community Cohort. J Gerontol A Biol Sci Med Sci 2020;20:1-2.
5. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. J Lipid Res 2009;50:S183-8.
6. Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Dudenkov TM, et al. *APOε4* is associated with enhanced in vivo innate immune responses in human subjects. J Allergy Clin Immunol 2014;134:127-34.
7. Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is *APOE*4* a 'thrifty' allele? Ann Hum Genet 1999;63:301-10.

RNA is not virus

To the Editor:

Yonker et al demonstrated high levels of viral RNA in nasopharyngeal samples obtained from children.[1] A plausible explanation for the seemingly counterintuitive lack of symptoms and high viral load is the methods employed are detecting high viral RNA, which does not correlate to high viral load as the authors suggest. Establishing a correlation between RNA and virus in the asymptomatic pediatric population with a virus culture is a prequisite for assertion that RNA positive children carry high viral loads.[2] An alternative explanation is that the children in the study, and generally most children, mount an effective immune response to subclinical infection. That immune response causes lysis of infected cells, spilling cellular contents including viral RNA and proteins into surrounding tissue or interference with viral assembly inhibiting excretion of infectious virus. High RNA in nasopharyngeal samples obtained from asymptomatic patients is a reflection of an effective immune response rather than high viral load, explaining minimal infectivity of such subjects.[3]

Gregory I. Sawchyn, MD, MBA
Population Health
Sound Physicians Group
Tacoma, Washington

https://doi.org/10.1016/j.jpeds.2020.09.057

The author declares no conflicts of interest.

References

1. Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. J Pediatr 2020;227:45-52.e5.
2. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 2020;39:1059-61.
3. Kim J, Choe YJ, Lee J, Park YJ, Park O, Han MS, et al. Role of children in household transmission of COVID-19. Arch Dis Child, in press.

Reply

To the Editor:

In our article, we report high viral load in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the first 2 days of illness. We did not assess the viability of virus from these respiratory secretions and agree that RNA does not necessarily correlate with live virus. However, in hospitalized adults, live virus is readily cultured from respiratory secretions during the first week of symptoms.[1] It is plausible that differences exists between pediatric and adult immune responses to SARS-CoV-2[2]; distinctions in mucosal immune responses could impact viral detection by reverse-transcription polymerase chain reaction and/or severity of symptoms. Another plausible hypothesis is that SARS-CoV-2 could colonize the upper airways efficiently in both children and adults but children may be less likely to have colonization in the lower respiratory tract. Although we described SARS-CoV-2 serology and show that infected children mount a humoral response following infection, we did not assess mucosal responses or regional differences of viral load within the airways. Research is needed to test these hypotheses.

Lael M. Yonker, MD
Alessio Fasano, MD
Mucosal Immunology and Biology Research Center
Department of Pediatrics
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

https://doi.org/10.1016/j.jpeds.2020.09.058

References

1. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.
2. Fialkowski A, Gernez Y, Arya P, Weinacht KG, Kinane TB, Yonker LM, et al. Insight into the pediatric and adult dichotomy of COVID-19: age-related differences in the immune response to SARS-CoV-2 infection. Pediatr Pulmonol 2020;55:2556-64.