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VIEWPOINT

Disparities in Susceptibility to Multisystem Inflammatory Syndrome in Children

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The COVID-19 pandemic has affected more than 29 million people in the US and caused more than 540 000 deaths as of March 2021 according to the US Centers for Disease Control and Prevention (CDC).¹ In adults, the most severe manifestation of COVID-19 is acute respiratory distress syndrome, which occurs most commonly among older individuals with underlying medical comorbidities. A notable feature of COVID-19 is that children have been relatively spared compared with adults, as children younger than 18 years only represent 11% of those with COVID-19 infection and 0.1% of deaths in the US.¹ A second notable feature of COVID-19 is that Black and Hispanic individuals bear a disproportionate burden of disease and adverse outcomes compared with White and Asian individuals, and unfortunately, children from racial and ethnic minority groups also bear this burden.¹ Black and Hispanic children are infected and die of COVID-19 at higher rates relative to their representation in the population and, strikingly, make up the overwhelming majority (66%) of those who develop a newly emerging life-threatening condition, multisystem inflammatory syndrome in children (MIS-C).^{1,2}

MIS-C was first reported in April 2020 after multiple previously healthy children presented with cardiovascular shock, fever, and hyperinflammation in the United Kingdom. In May 2020, the CDC issued a national health advisory for MIS-C, which is now characterized by fever, multiorgan (2 or more) system involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, derma-

tologic, or neurologic), and clinically severe illness requiring hospitalization.^{2,3} The etiology of MIS-C seems to be postinfectious, as most children with MIS-C test positive for antibodies against SARS-CoV-2.²⁻⁴ Cellular profiling in children with MIS-C has revealed an immune-driven pathophysiology, evident by drastic elevations in inflammatory mediators and a distinct immune signature suggestive of lymphocytic and myeloid activation and mucosal immune dysregulation.⁴ Interestingly, autoantibodies have also been implicated in disease pathogenesis, as autoantigen reactivity to endothelial, gastrointestinal, and immune cell antigens can be detected in plasma in children with MIS-C.⁴ Although we suspect that MIS-C is driven by an aberrant immune response to SARS-CoV-2 infection, we still do not know why some children are susceptible to MIS-C after SARS-CoV-2 infection while others are not. Furthermore, the cause for differential rates of MIS-C among Black and Hispanic children remains unclear.

When examining the disproportionate burden of COVID-19 cases in Black and Hispanic adults, differences in access to health care and social and structural inequities driven by racism in the US likely account for most differences, yet it is unclear how well these factors explain the disparities we see in children. A leading explanation for the disproportionate burden of COVID-19 among Black and Hispanic adults is a high incidence of underlying comorbidities known to increase risk of COVID-19 complications, including diabetes, obesity, and kidney disease,⁵ which are likely related to structural factors

including health care inequity and food insecurity. However, underlying comorbid disease does not appear to be a contributing factor in MIS-C, as most affected children were previously healthy.^{2,3} A second leading explanation for COVID-19 disparities in adult populations is high-density living conditions and employment in occupations that require frequent in-person interactions; this certainly extends to children living in the same households and is probably an important driving force of the higher-than-expected incidence of MIS-C.⁶ A third probable explanation is the experience of bias, discrimination, and racism faced by Black and Hispanic communities and the long history of medical mistreatment of Black individuals in the US, potentially leading to justified distrust of the health care system, delays in seeking care, differences in quality of care, and greater morbidity and mortality; this also likely extends to children, although it is unclear how this might influence the disparities observed in MIS-C.

The effect of social inequity on health care outcomes for Black and Hispanic children in the US is undeniable; however, social determinants may not completely explain disproportionate MIS-C incidence. Recent evidence suggests that increased risk of MIS-C in Black and Hispanic children might extend beyond socioeconomic status after adjusting for neighborhood and social vulnerability index.⁶ Complex socioeconomic factors clearly affect risk for MIS-C, yet it is highly conceivable that biologic variation confers individual differences in immunologic responsiveness to SARS-CoV-2 infection,⁷ as the clinical response ranges from asymptomatic carriage to severe hyperinflammation and multiorgan failure. Moreover, the fact that MIS-C can cause critical illness and death in otherwise healthy children for reasons we cannot explain stresses the need for research focused on evaluating additional factors to identify children at highest risk.

The extent to which genetics is associated with the development of MIS-C is currently unknown. Genome-wide association studies (GWASs) of Kawasaki disease, a small-vessel vasculitis that presents similarly to MIS-C with hyperinflammation, set a precedent for investigating the effect of genetic predisposition in inflammatory syndromes, as the incidence of Kawasaki disease is significantly higher in children of Asian ancestry, and several gene variants/polymorphisms have been associated with disease.⁸ GWAS approaches are based on the understanding that many complex disorders are associated with multiple genetic polymorphisms that alter gene expression, which may potentially lead to immunologic variation and differential risk of inflammatory or infectious diseases.⁹ GWAS approaches have revealed that many autoimmune conditions, such as systemic lupus erythematosus and inflammatory bowel disease, are associated with gene variants that

appear to predispose susceptible individuals to mount an abnormal immunologic response to infectious or environmental exposures.⁹ Perhaps some children are more likely to develop MIS-C when genetic or immunologic predisposition intersects with environmental factors or socioeconomic risk. This possibility justifies the need for in-depth investigations of the interplay between the virus, immune system, genetics, and environment to fully understand the causes of differences in MIS-C susceptibility. While GWAS approaches may help identify genetic variants associated with MIS-C, it is important to note that most genetic studies have few participants of non-European ancestry, implying that results from existing genetic studies may not be generalizable or clinically relevant to individuals of African and Hispanic descent. Improved representation in genetic studies may potentially reveal novel genetic associations that are also clinically relevant.¹⁰

Although the immunologic consequences of genetic variation have been described,⁹ the causes of genetic variation are less clear. Regulation of gene expression is influenced by epigenetic processes; therefore, it is plausible that gene variation is driven by individual differences in psychosocial or environmental exposures, such as toxic stress, disparate living conditions, vaccination or infectious history, and diet, which can vary based on culture, ethnicity, and socioeconomic status. The development of models that may predict individual risk by weighing environmental exposures alongside genetic predisposition may help identify key drivers for MIS-C susceptibility by predicting the likelihood of adverse outcomes after SARS-CoV-2 infection.⁵

Overall, disparities in susceptibility to COVID-19 are multifactorial and partly associated with social inequity.^{5,6} Investigating the relative contribution of genetic variation in immune responses to SARS-CoV-2 infection may help guide the development of risk stratification tools and targeted therapies. To identify genetic variants that are potentially predictive of disease susceptibility, large genotyping studies are necessary and should aim to include individuals of diverse ancestral backgrounds, as limited diversity in genomic studies may impede our ability to fully understand how genetic, ancestral, and environmental factors affect disease and may further exacerbate existing health disparities. Such studies may ultimately require international collaborations to collect sufficient sample sizes to derive meaningful conclusions. These efforts must also consider the full spectrum of systemic factors and account for the effects of social determinants of health on disease risk, which calls for collaborative efforts between scientists, physicians, and policy makers. Above all, our collective goal should be to reduce MIS-C incidence and mortality by any means necessary and to achieve greater equity in the care of pediatric populations that are most vulnerable.

ARTICLE INFORMATION

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