

Rapid Reviews COVID-19

Review 2: "Cytotoxic lymphocytes are dysregulated in multisystem inflammatory syndrome in children"

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RR:C19 Evidence Scale rating by reviewer:

Not informative. *The flaws in the data and methods in this study are sufficiently serious that they do not substantially justify the claims made. It is not possible to say whether the results and conclusions would match that of the hypothetical ideal study. The study should not be considered as evidence by decision-makers.*

Review:

We read with interest the article “Cytotoxic lymphocytes are dysregulated in multisystem inflammatory syndrome in children” by Beckmann et al. The authors should be congratulated for tackling such an important question. The authors studied the blood transcriptomes of multisystem inflammatory syndrome in children (MIS-C) cases, pediatric cases of 2019 coronavirus disease (COVID-19), and healthy controls to help identify genes, pathways and cell types driving MIS-C. They found that MIS-C transcriptional signature partially shared with the transcriptional response to SARS-CoV-2 infection and the signature of Kawasaki disease (KD) but not other pediatric inflammatory conditions, or classic autoimmune diseases.

Early in the pandemic, we were worried that cases of KD might be missed.¹ Little did we know that few days after the call for action was published, cases of a new inflammatory illness linked to COVID-19 with features similar to KD, now termed MIS-C, would emerge.² Debate continues to exist: Is MIS-C a form of KD? ^{3,4} Ongoing efforts to establish multicenter national and international registries should be encouraged to help provide a larger cohort to assess the immunopathophysiologic mechanism of MIS-C. Beckmann et al. suggested that dysregulated cytotoxic lymphocyte response to SARS-Cov-2 infection is seen in children who developed MIS-C.

One limitation in this study is small sample size. Only 8 specimens from 8 individuals with MIS-C, 18 specimens from 7 pediatric COVID-19 individuals and 4 specimens from 4 healthy controls were studied. A second limitation is the use of varied immune modulating medications. The authors note that none of the individuals with MIS-C were taking chronic immunosuppressive medications at time of sample collection, but no mention is made about dose or timing of acute therapies (e.g. steroids or IVIG) to treat MIS-C symptoms. Six out of the 7 individuals in the COVID-19 group were taking immunomodulatory medications (i.e. chemotherapy, tacrolimus, steroids or infliximab). Moreover, individuals in the comparator group had known immune-related comorbidities, including leukemia and inflammatory bowel disease. This represents a suboptimal collection of subjects and comparator group, as both the underlying immune dysregulation disease and prior/current medication interventions have marked potential to influence gene expression and cell phenotype.^{5,6}

The authors used RNA sequencing (RNA-seq) of whole blood from 8 individuals with MIS-C, 7 individuals with COVID-19 and 4 healthy controls to associate gene expression with disease. They report a "MIS-C signature" cluster of downregulated genes, which code for exhausted CD8+ T-cells and CD56^{dim}CD57+ NK cells, leading to pathway dysregulation. The use of whole blood for RNA-seq, with phenotype relevant gene filters, has been shown to identify causal gene variants or highlight candidate genes. The success rate of gene identification using this method is thought to be less than 17%, and is contingent on prior knowledge of phenotype and candidate genes.⁷ As such, it is notable that their use of probabilistic causal networking revealed 9 different genes, driving MIS-C pathogenesis.

Other considerations:

- 1- Please clarify Figure 1. Why did you state Table 1 in Figure 1A? Mentioning other graphs within each is confusing. Please explain the change in color.
- 2- The "large cohort of individuals with inflammatory bowel disease", the 78 KD patients and 55 controls from 2018 and other disease cohorts like 918 cases and 263 controls for autoimmune disease were not mentioned in abstract.
- 3- Healthy controls were not in the pediatric age range. ³/₄ of the healthy control were white adults. The majority of the MIS-C and COVID-19 patients were non-white. Please choose a better control.
- 4- In the table, why did you give age range? Why not give actual age?
- 5- We had no access to Data S1.
- 6- Some of the information in the results belong to methods section. The paper is not organized in the usual introduction, method, results and discussion sections.
- 7- None of the figures were identified, i.e. no title associated.

References:

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