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.

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Letter to the Editor

IFN-α levels in ruxolitinib-treatead Aicardi-Goutières patient during SARS-CoV-2 infection: A case report

Sir

The article by Vlachogiannis et al. published online in the February issue of your Journal suggests that changes of Adenosine -to-Inosine (A-to-I) could affect the inflammatory responses against SARS-CoV2 [1]. There is evidence that inactivating mutations of the gene encoding adenosine deaminase specific for dsRNA (ADAR) which deaminates adenosine in dsRNAs to inosine are causative of one form of Aicardi–Goutieres syndrome (AGS4) characterized by induction of IFNs, IFN-stimulated genes, cerebral white matter abnormalities with basal ganglia calcification, cerebral atrophy, and chronic cerebrospinal fluid (CSF) lymphocytosis [2,3].

We herein report the case of two siblings with AGS4 due to compound heterozygous mutations in ADAR gene: one 5-year-old female who was under treatment with ruxolitinib, subcutaneous immunoglobulin, who developed COVID-19 with mild manifestations and her 13 yo brother.

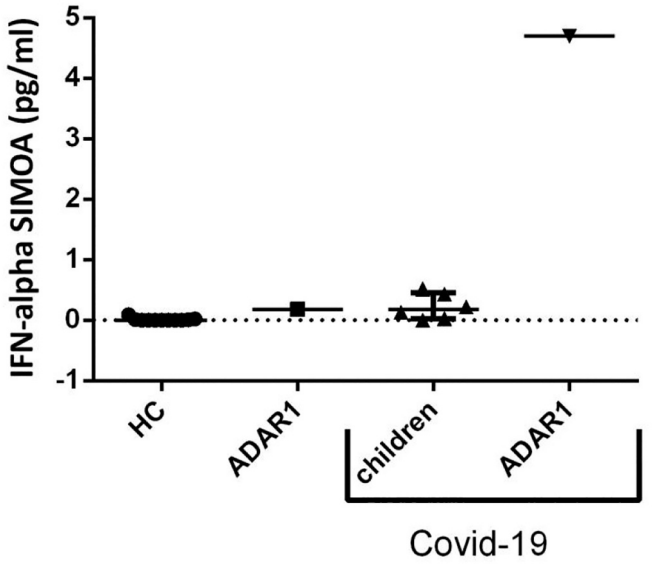

Fig. 1. Analysis of plasmatic levels of IFN-alpha in a 5 years old child affected with AGS4 during COVID19 in comparison to levels measured in eight healthy donors, her brother with AGS4 while healthy (without SARS-CoV2 infection) and six children during COVID19.

In January 2021 she presented fever for two days and cough. Three days after the appearance of symptoms, analysis of SARS-CoV-2 by real time PCR of nasopharyngeal swab revealed COVID19 in the younger sibling, but not in her older brother. The course of the disease was mild, with normal respiratory function and normal blood oxygen saturation without need of oxygen supplementation. White cell counts, Erythrocyte Sedimentation Rate, and C-Reactive Protein were also normal, while chest-X-ray showed only a minimal signs of interstitial pneumonia. Analysis of plasma levels of IFN-α by ultrasensitive immunoassay (Simoa, Quanterix) two days after admission showed high levels of the cytokine (4.69 pg/ml), as compared to previous measurement performed one month before the infection (<0.001 pg/ml), or to levels measured in her brother (0.184 pg/ml) who was not infected by SARS-CoV2. In addition, comparison of plasmatic IFN-alpha concentrations in the two siblings with levels measured in healthy donors or in children with COVID-19 showed higher concentration of the cytokine in the child with AGS4 affected by COVID-19 (Fig. 1). Expression of IFN-stimulated genes, which increased during the infection as measured by interferon score, was about 296.01 fold higher than levels measured in healthy control subject. Finally, blood test performed one month after SARS-CoV-2 infection showed high levels of anti-SARS-CoV2 IgG (71 AU), while IFN-α blood levels returned to normal.

There is evidence that mutations affecting genes encoding molecules involved in type I interferon pathway are associated with increased susceptibility to SARS-CoV2 and can be linked to severe outcome [4]. Detection of significant plasmatic levels of IFN-alpha in a child with AGS4 infected by SARS-CoV2 supports the hypothesis that ADAR inactivation during infection by this virus in AGS4 patients can result in decreased ADAR1 activity and higher expression of type I interferons. It is tempting to speculate that higher levels of type I interferons might be linked to a benign disease and that targeting ADAR1 expression in COVID19 patients might favorably affect host immune response against the virus.

References

[1] N.I. Vlachogiannis, K. Verrou, K. Stellos, P.P. Sfikakis, D. Paraskevis, The role of A-to-I RNA editing in infections by RNA viruses: possible implications for SARS-CoV-2 infection, Clin Immunol 226 (2021) 108699.
[2] Y.J. Crow, J. Rehwinkel, Aicardi-Goutie'res syndrome and related phenotypes: linking nucleic acid metabolism with autoimmunity, Hum Mol Genet 18 (R2) (2009) 130–136.
[3] D. Tonduti, E. Fazzi, R. Badolato, S. Orcesi, Novel and emerging treatments for Aicardi-Goutières syndrome, Expert Rev Clin Immunol 16 (2) (2020).
[4] Q. Zhang, Z. Liu, M. Moncada-Velez, et al., Inborn errors of type I IFN immunity in patients with life-threatening COVID-19, Science (80-) 370 (6515) (2020).

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