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## Marked changes in innate immunity associated with a mild course of COVID-19 in identical twins with athymia and absent circulating T cells

*To the Editor:*

We read with interest the recent articles from Zhang et al and Bastard et al revealing impaired type I IFN immunity as a major risk for severe coronavirus disease 2019 (COVID-19)[1,2]; however, the relative importance of innate and adaptive immunity for viral control is difficult to evaluate.[3] A diagnosis of mild COVID-19 in 2 identical twin neonates with an uncommon primary immunodeficiency (PID) that causes athymia and almost complete T-cell lymphopenia allowed study of innate immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the absence of adaptive immunity.

Identical male twins were born at 36+4 weeks of gestation to nonconsanguineous parents. Diarrhea in both prompted admission to the neonatology department. Routine cerebral ultrasounds revealed white matter hyperechogenicity in both, and congenital cytomegalovirus (CMV) was diagnosed. At 13 days of life, both presented self-limited fever and mild cough and nosocomial SARS-CoV-2 infection was suspected and PCR confirmed. Unfortunately, the PCR-positive samples were not stored, and so a more detailed molecular characterization of the virus in these infants is impossible. The absence of a detailed virological analysis of the SARS-CoV-2 detected in these children and the possible confounding effects of coinfection with human cytomegalovirus (HCMV) are important limitations of this report.

Detailed immunologic evaluation identified a $T^-$ $B^+$ natural killer $(NK)^+$ phenotype (Fig 1, *A*), with no recent thymic migrants. Retrospective analysis of Guthrie cards revealed undetectable T-cell receptor excision circles (*TRECS*), but normal kappa-deleting recombination excision circles (KRECS). Absent thymic shadow, central nervous system lesions, and inner ear malformations in magnetic resonance imaging (MRI), hypoparathyroidism, severe hypocalcemia, and hyperphosphatemia suggested Di George syndrome. Analysis of a customized Next-Generation Sequencing (NGS) panel for primary immunodeficiencies identified a mutant *TBX1* gene allele with c.1170_1176del, p.G391PfsTer67 and c.1163C>T, p.A388V *de novo* variants (pathogenic and probably pathogenic, respectively). No other pathogenic variants were found in known genes associated with immunodeficiency.

Surprisingly, clinical signs of SARS-CoV-2 infection resolved within 2 weeks, with negative PCRs. Because almost no T cells, and only naive B cells, were present, innate immunity to SARS-CoV-2 was investigated. A strong signature of type I interferon-stimulated genes (ISGs) (Fig 1, *B*) was detected in blood cells, which diminished rapidly, notwithstanding persistent CMV replication despite antiviral treatment (supplementary data available on request). These data suggest that ISG induction was likely driven by SARS-CoV-2, rather than CMV, infection; however, in the absence of data from other SARS-CoV-$2^+$, $CMV^-$, T-cell–deficient newborns, we cannot completely exclude that either the treatment or the CMV infection itself may have modulated some ISG expression. Indeed, it is possible that the congenital CMV infection primed innate immunity for more effective suppression of SARS-CoV-2 replication.

No marked changes in major lymphocyte populations were noted (Fig 1, *C*) until 26 days after positive PCR, when a population of activated NK cells appeared in peripheral blood (supplementary data available on request). Strikingly, upregulation of the NKG2C receptor on essentially all $CD56^{dim}$ NK cells was observed (Fig 1, *D*) that generally did not coexpress CD57, unlike the NKG2C-expressing NK cells associated with CMV infection.[4] The spontaneous recovery of these T-cell–deficient infants from SARS-CoV-2 infection supports the idea that innate immune mechanisms are important for immune control of this virus.[1,2,5]

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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https://doi.org/10.1016/j.jaci.2020.11.007

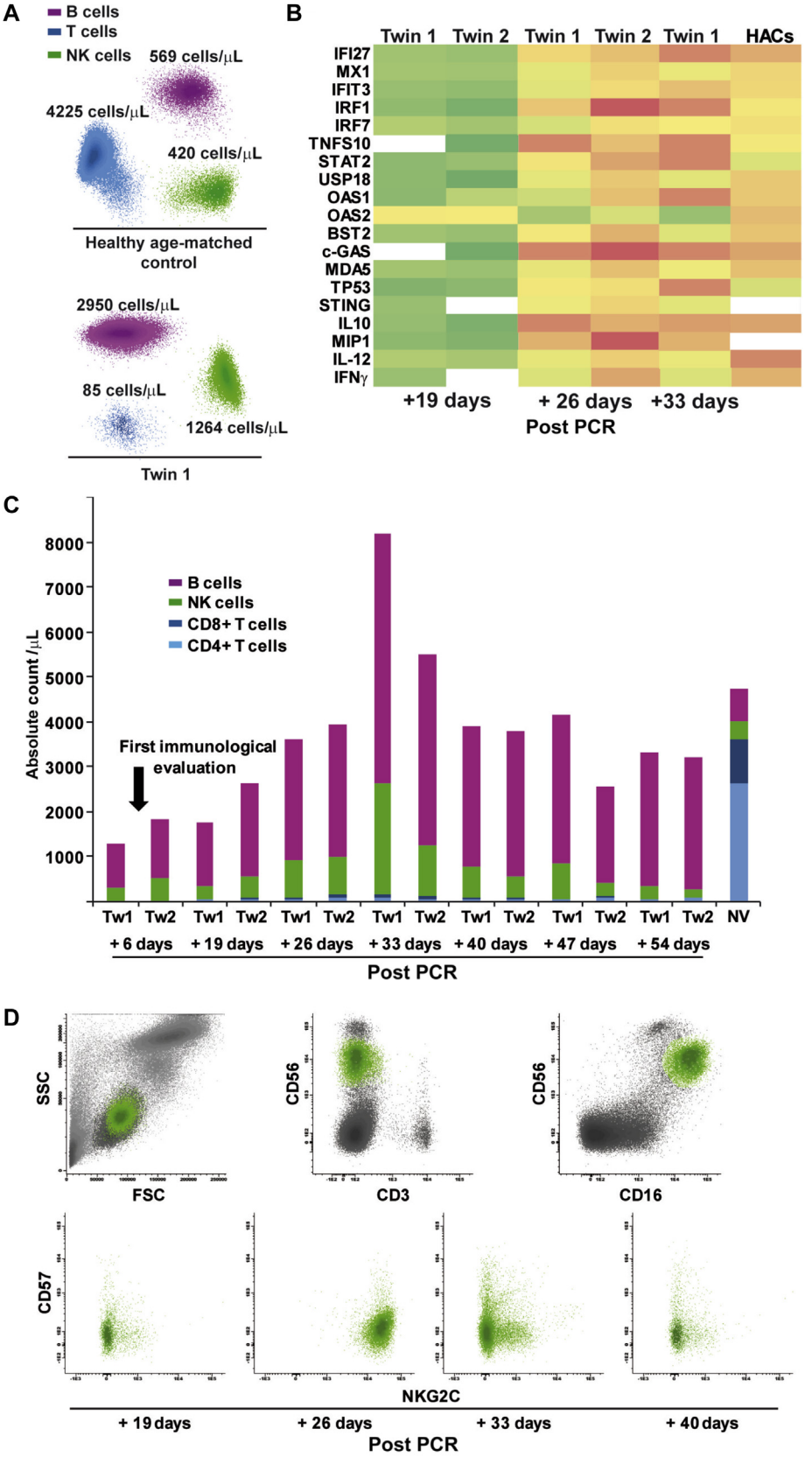


**FIG 1.** Prospective flow cytometric and molecular studies in peripheral blood after positive SARS-CoV-2 PCR result: **A,** Automated population separator (APS) diagram of major lymphocyte subpopulations in a representative study of one of the patients, showing persistent almost complete T-cell lymphopenia. **B,** Expression of a set of IFN-αβ ISGs in whole blood; green color represents increased expression; HACs, average value of 4 healthy adult controls. **C,** Absolute numbers of lymphocyte subpopulations in both twins. **D,** Dot-plots of immune phenotyping showing transient increase in $CD3^{-}CD56^{dim}CD16^{+}NKG2C^{+}CD57^{-}$ NK cells. *FSC*, Forward scatter; *HAC*, Healthy adult control; *NV*, normal values; *SSC*, side scatter; *Tw*, twin.