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Additional hypotheses about why COVID-19 is milder in children than adults

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We read with great interest the editorial by Brodin discussing why COVID-19 appears to be so mild in children.[1] In particular, the author discussed the potential theories that could explain why children have a lower incidence and milder clinical manifestations than adults. However, we feel it is important to present some other additional hypotheses in order to address all the potential theories.

In the last SARS-CoV epidemic in 2002, milder clinical manifestations were observed in children and it was hypothesised that children's vaccines could have induced cross reactivity against SARS-CoV.[2] Unfortunately, this hypothesis was not confirmed and other factors, namely the inability to mount a hormone response or upregulation of some ant-inflammatory cytokines, were presented to explain the phenomenon.

However, we probably need to consider another theory. Ageing is associated with a progressive decline in the normal functioning of the immune system, which leads to weaker immune responses and impairs a person's ability to respond to new stimulants. This process involves the natural involution of the thymus, starting during or soon after the first year of birth. It then shows an accelerated decline after puberty, and the thymic microenvironment cells continue to reduce by 3% to 5% a year until approximately 30-40 years of age before slowing down to less than 1% per year.[3] After the fourth and fifth decade of life, the involution of the thymus leads to a significant decline in naïve T cell output. This affects the composition of the peripheral CD4 and CD8 T-cell pool and has a negative influence on the adaptive immunity that is considered to be the leading cause of morbidity and mortality in the elderly.[4] By comparing the CD4 and CD8 T-cell phenotypic and functional changes with ageing, CD8 T cells appear to be more susceptible to age for different functional subsets, with a more pronounced education of their naïve cells and functional memory subsets. Within the T-cell subset, a stronger reduction of CD8, compared with CD4, lymphocytes is associated with an increased CD4/CD8 ratio. CD8 T cells have a fundamental role in disease control and the clinical outcomes of many viral infections than CD4 T cells.

The function of the CD8 T cells is to participate in antiviral immunity by recognising and destroying virus-infected cells by cell lysis and producing toxic chemokines. This avoids the further spread of the viral infection.

Emerging data from the COVID-19 outbreak in Wuhan, China, suggest that the number of T cells was significantly decreased in patients affected by the disease, suggesting that dysregulation of the immune response involving T lymphocytes was present in this pathological infection.[5]

In our opinion, the functional and phenotypic features of children's immune systems should be included when explaining their age-dependent susceptibility to COVID-19 and the severity of any disease.

CONFLICTS OF INTEREST

None.

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