Paediatric Long COVID as a Window into Post-Viral Remodelling and Immune-Metabolic Resilience

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Paediatric long COVID provides a rare opportunity to uncover fundamental principles of post-viral recovery and failed resolution. Because age-tuned paediatric immunity is less overlaid by decades of immune imprinting, comorbid inflammation and immunosenescence, children may reveal protective and pathogenic mechanisms that are more difficult to resolve in adults. In this view, paediatric long COVID is not a single disease mechanism, but a biological framework to understand how time, viral history and immune-metabolic resilience shape recovery after infection.

Using deep longitudinal phenotyping of children and adolescents with severe long COVID and controls, we identified temporally structured immune-metabolic trajectories rather than a uniform inflammatory signature. Early disease was characterized by waning antiviral activity together with type-2 and innate immune activation, whereas persistent disease shifted toward innate and Th2/Th17-associated patterns. Viral immune history further shaped these trajectories, with prior EBV exposure marking a distinct inflammatory subgroup characterized by enhanced innate cytokines, IL-12/IL-23-axis activity and granulocytic alterations.

Within the EBV-naïve or EBV-low subgroup, we further identified potential immune-metabolic resilience axes, including IL-12p40, thiamine and basophils, that were associated with milder functional impairment. Together, these findings suggest that paediatric long COVID can serve as a window into post-viral immune imprinting, failed resolution and protective resilience. This perspective may help move the field from symptom-based definitions toward biomarker-guided stratification and recovery-oriented interventions.

Together, these findings position paediatric long COVID as a biologically informative model of post-viral immune remodelling. They suggest that recovery after infection is not merely the absence of inflammation, but an actively regulated immune-metabolic state shaped by prior viral imprinting and resilience programmes.