Biphasic Variation Over Time in Presenting Features of Patients With COVID-19

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Current data suggest lower rates of severe coronavirus disease 2019 (COVID-19) in children compared with adults.[1,2] Although severe respiratory disease has rarely been described,[3] new data suggest the emergence of a COVID-19–related multisystem inflammatory syndrome in children (MIS-C).[4,5] Describing the temporal variation of pediatric COVID-19 presentations across the course of a high-prevalence outbreak may help elucidate the epidemiology and biology of these manifestations in children.

METHODS

We conducted a retrospective chart review of children (age ≤20 years) presenting to the New York-Presbyterian Morgan Stanley Children's Hospital pediatric emergency department from March 13, 2020 (date of first known case), to May 19, 2020, who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 testing included reverse transcriptase polymerase chain reaction (PCR) done on nasopharyngeal swabs (cobas 6800 [Roche Diagnostics, Basel, Switzerland] or GeneXpert Infinity Systems [Cepheid, Sunnyvale, CA]) or serology (a NY State Department of Health–approved combined immunoglobulin G and immunoglobulin M immune assay against SARS-CoV-2 spike trimer or nucleocapsid protein). Serology was only performed when there was clinical suspicion for SARS-CoV-2–related disease and negative PCR results. Only presentations at the time of initial test positivity were assessed.

Across each week of the study period, we calculated (1) mean viral load, (2) mean initial C-reactive protein (the inflammatory marker routinely used at our center), and (3) proportions of cases with specific presenting symptomatology.

Viral load in positive nasopharyngeal samples was measured by using the inverse of cycle threshold values of the envelope protein, the most consistently amplified viral target. Hypoxemia was defined as oxygen saturation ≤94% at presentation. Presenting symptomatology was classified by review of initial admission records as recorded by the treating physician. Symptoms were classified into 4 distinct groups: respiratory (dyspnea, chest pain, cough, nasal congestion), gastrointestinal (abdominal pain, vomiting, diarrhea), mucocutaneous (sore throat, lip redness, rash, conjunctivitis), and neurologic (headache, seizure, altered mental status, cranial nerve VI palsy). Symptom duration was not assessed. Mantel-Haenszel linear-by-linear associations were examined to examine changes in presentation over time. All study activities were approved by the Columbia University Irving Medical Center Institutional Review Board.

RESULTS

In total, 106 children with COVID-19 presented in 2 distinct 5-week phases

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Drs Zachariah and Carter conceived of the presented concept, reviewed the collected data, and contributed to the data analysis, interpretation, development of figures, and writing and critical review of this manuscript; Dr Jamal collected the data and contributed to the data analysis, interpretation, development of figures, and writing and critical review of this manuscript; Dr Whittier provided the viral load data and contributed to the data analysis, interpretation, development of figures, and review of this manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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(Fig 1A). Hospitalization rates remained stable (Fig 1A).

Although mean age was stable over the study period, the proportion of patients <12 months of age decreased over time (P = .001) from 22.2% to 71.4% over phase 1 to 4.5% to 16.7% in phase 2. Mean nasopharyngeal viral loads (n = 88) decreased over time, whereas mean initial C-reactive protein concentrations (n = 83) increased in the second phase (Fig 1B). Positive serology results were only seen in phase 2, during which 25 children had positive serology testing results and 29 had positive PCR results.

Fever was prevalent throughout but more common in phase 2 (Fig 1C). Hypoxemia and dyspnea predominated early, followed by a striking increase in gastrointestinal and mucocutaneous symptoms (Fig 1 C and D). In phase 1, mucocutaneous complaints were limited to sore throat, whereas rash and conjunctivitis were present exclusively in phase 2. Neurologic symptoms increased over time, with headache presenting throughout but altered mental status and cranial nerve VI palsy exclusively presenting in phase 2.

DISCUSSION

These data reveal a biphasic nature of disease presentation in a high-prevalence SARS-CoV-2 outbreak in susceptible children. The first phase is consistent with uncontrolled community spread followed by a drop in new infections after local nonpharmaceutical interventions (school closures and shelter-in-place orders) were instituted. The second phase reflected a resurgence of disease while nonpharmaceutical intervention measures were still in place and local new infection rates had markedly dropped.[6] Notably, viral

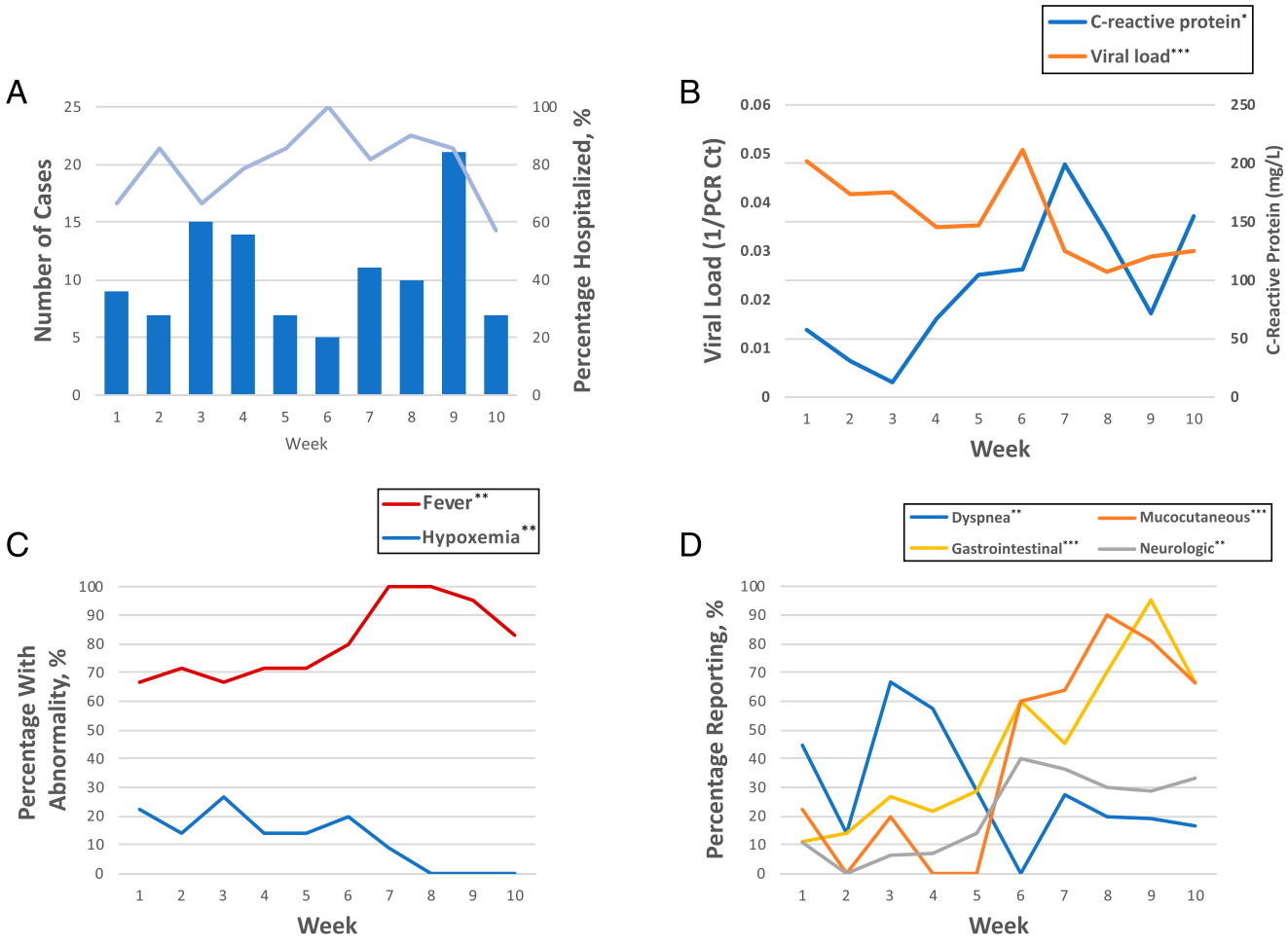

FIGURE 1

Trends in initial clinical and laboratory features (N = 106). A, Case numbers (bars) and proportion hospitalized (line). B, Initial inflammatory markers (n = 83) and viral load (n = 88) by week (P values for week are from analysis of variance). C, Presentation vital sign abnormalities by week (P values from Mantel-Haenszel linear-by-linear association term). D, Presenting symptomatology by week (P values from Mantel-Haenszel linear-by-linear association term). *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$. Ct, cycle threshold.

load measures in our cohort decreased in the second phase to levels more consistent with remote rather than active infection,[7] whereas mean inflammatory markers were higher, indicating more severe systemic inflammation. Our findings suggest 2 phases of immune response to initial SARS-CoV-2 infection in susceptible children: acute COVID-19 with predominantly respiratory symptoms and a delayed postinfectious hyperinflammatory phenomenon with gastrointestinal, mucocutaneous, and neurologic symptoms, recently described as MIS-C.

Although both of these presentations have been previously described, our data reveal a distinct epidemiological time course with clear trends in presenting symptomatology, inflammatory markers, and viral load. These presentations occurred in different children as no patients diagnosed in phase 1 returned with MIS-C symptoms.

Although recognition of MIS-C may have increased over the study period, per state requirements, we reviewed all emergency department visits and hospitalizations for presentations compatible with possible MIS-C and found only 1 patient in phase 1 who had Kawasaki disease and negative SARS-CoV-2 testing results. Surveillance for these distinct acute versus delayed COVID-19–related disease phenotypes may help epidemiologists assess onset and intensity of ongoing community transmission and may have implications for emergency preparedness for recurrent waves of SARS-CoV-2 in terms of ensuring supply of relevant medications (eg, remdesivir versus intravenous immunoglobulin) and supportive interventions (eg, ventilators versus circulatory support). Furthermore, in geographic regions in which infection trends may be less distinct, presenting symptomatology, inflammatory markers, and viral loads could help clinicians to distinguish between these pediatric manifestations of COVID-19.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
MIS-C: multisystem inflammatory syndrome in children
PCR: polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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