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Human Parechovirus Central Nervous System Infection in a Young Infant Cohort

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the test for these viruses are excellent (>95% and in some studies close to 100%), the sensitivities are not optimal (between 75% and 95%).[14,15] However, if the sensitivity seems to be better in children than adults, we have certainly underestimated the burden of these viruses and particularly RSV. Different clinical situations (e.g., clinical laboratory of the hospital vs. ambulatory care) will require different diagnostic solutions, considering the ease of sample collection, the absence of equipment, the time of the result and especially the cost. In ambulatory pediatrics, the rapid antigen test seems an acceptable compromise: the use of rapid antigen tests optimized and facilitated enrollment in primary care. The second limitation is the absence of data before the COVID-19 pandemic. Nonpharmaceutical interventions have induced major RSV epidemiological changes, and long-term RSV surveillance would help support our findings.

In conclusion, surveillance systems may need to consider continuous surveillance to accurately capture and describe RSV circulation in the COVID-19 era, especially to inform the start of immunoprophylaxis against RSV. Monitoring multiple viruses (RSV, influenza, SARS-CoV-2) may help optimize the value of year-round surveillance systems.

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HUMAN PARECHOVIRUS CENTRAL NERVOUS SYSTEM INFECTION IN A YOUNG INFANT COHORT

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Abstract: In 2022, a surge in cases of pediatric human parechovirus (HPeV) central nervous system infections in young infants was seen at our institution. Despite the dramatic increase in the number of cases seen that year, the clinical features of the illness were similar to prior years. The recent pediatric HPeV surge highlights the need to evaluate treatment options and standardize follow-up to better understand the long-term prognosis of infants with HPeV infection.

Key Words: infants, neonates, human parechovirus, CNS, immunoglobulin

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TABLE 1. Characteristics of the 2 Cohorts of Neonates and Infants With Parechovirus Central Nervous System Infection

Variable	Group 1, N = 9 (January 2018 to December 2021)	Group 2, N = 22 (January 2022 to October 2022)	*P* value*
Age on admission, in days, mean ± SE mean	24.5 ± 7	18.9 ± 2.9	NS
Male, n (%)	7 (77.8%)	8 (36.4%)	NS
Preterm (<36 weeks), n (%)	0 (0%)	1 (4.6%)	NS
Length of stay, days, median (IQR)	3 (2, 4)	4 (3, 5)	0.01
ICU admission, n (%)	4 (44.4%)	10 (45.5%)	NS
Weight in grams on admission, mean ± SE mean	4098 ± 250	4098 ± 128	NS
Infants with older children attending day care (in the same household), n (%)	9 (100%)	18 (90%)	NS
Signs and symptoms, n (%)			
Fever	8 (89%)	22 (100%)	NS
Duration of fever in days, median (IQR)	2 (2, 3)	3 (2, 3.25)	NS
Rash	3 (33.3%)	2 (9.1%)	NS
Respiratory infection symptoms‡	0 (0%)	5 (22.7%)	NS
Gastrointestinal symptoms†	6 (66.7%)	14 (63.6%)	NS
Irritability/fussiness	8 (88.9%)	21 (95%)	NS
Altered level of responsiveness	3 (33.3%)	11 (50%)	NS
Seizures	1 (11.1%)	3 (13.6%)	NS
CSF characteristics, mean ± SE mean			
WBC count/μL	8 ± 1.9	4.2 ± 0.7	NS
Glucose (mg/dL)	51.2 ± 2.5	60 ± 1.8	<0.01
Protein (mg/dL)	59.5 ± 11.7	101 ± 28.3	NS
Other labs, mean ± SE mean			
WBC cells/nL on admission	6.4 ± 1	5.4 ± 0.4	NS
Hb g/dL on admission	13.1 ± 0.7	13.1 ± 0.5	NS
PLT cells/nL on admission	272 ± 26.7	285 ± 16.7	NS
AST U/L highest during hospitalization	125 ± 31.8	80.5 ± 14.3	NS
ALT U/L highest during hospitalization	85.7 ± 44.5	55 ± 11.7	NS
CRP mg/L highest, n, mean ± SE mean	3, 2 ± 1	14, 6.6 ± 0.9	0.01
Required oxygen, n (%)	2 (22.2%)	7 (31.8%)	NS
Given IVIG, n (%)	0 (0%)	7 (31.8%)	NS
Given antibiotics, n (%)	8 (88.9%)	21 (95.5%)	NS
Given antiseizure medication, n (%)	1 (11.1%)	1 (4.5%)	NS

*Results are expressed as mean ± SEM or as percentage. Analysis of continuous variables was conducted using Student's *t* test or the Mann–Whitney *U* test for normally distributed and non-normally distributed variables, respectively. Categorical variables were compared by using the χ^2 or Fisher exact test, as appropriate. Statistical significance was assumed for $P < 0.05$.

†Gastrointestinal symptoms include abdominal distention, decreased oral intake, emesis and diarrhea.

‡Respiratory symptoms include nasal congestion, rhinorrhea and cough.

NS, $P > 0.05$; ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein; Hb, hemoglobin; IVIG, intravenous immunoglobulin; PLT, platelets; WBC, white blood cells.

Human parechoviruses (HPeVs) are small RNA viruses that belong to the same taxonomic family as enteroviruses and rhinoviruses. Most cases of HPeV infections occur in children causing mild upper respiratory or gastrointestinal symptoms. In younger infants, HPeV infections typically present as a febrile illness, exanthem, sepsis-like syndrome or with central nervous system manifestations (CNS).[1] HPeV has been an emerging cause of severe infections in young infants, likely because of improved detection methods.[1] Our institution noted an unusually high number of HPeV CNS cases beginning in May 2022 and reported this increase to the State Department of Health. In July 2022, the Centers for Disease Control and Prevention issued a health advisory warning to clinicians about the increased circulation of HPeV among young infants in the United States. We then sought to compare the cohort of infants with HPeV CNS infection seen between June and October 2022 to those seen in prior years with respect to clinical presentation, severity and prognosis.

METHODS

As part of sepsis evaluation, a lumbar puncture was performed for infants less than 1-month-old and for older children when clinically indicated. All children who tested positive for HPeV in the cerebrospinal fluid (CSF) through the multiplex molecular polymerase chain reaction panel (BioFire FilmArray Meningitis/Encephalitis Panel, bioMerieux) from January 2018 to October 2022 were included. We compared infants presenting between January 2018 and December 2021 (group 1) to those presenting between January 2022 and October 2022 (group 2). A retrospective medical record review was performed documenting presenting symptoms, preexisting morbidities, demographics, sick contacts, laboratory and imaging findings, management and outpatient follow-up. Data were collected in a standardized collection tool in the Research Electronic Data Capture system.[2] The Institutional Review Board approved this study. Results are expressed as mean ± SEM or as percentage. Analysis of continuous variables was conducted using Student's *t* test or the Mann–Whitney *U* test for normally distributed and non-normally distributed variables, respectively. Categorical variables were compared by using the χ^2 or Fisher exact test, as appropriate. Statistical significance was assumed for $P < 0.05$.

RESULTS

Between January 2018 and December 2021 (ie, 48 months) a total of 9 HPeV CNS cases were detected (0.2/month) versus 22 cases between January and October 2022 (ie, 10 months, 2.2/month). Overall, the highest numbers were detected during the summer months (June–July–August) accounting for 77% (24/31) of the study population. The seasonal and chronological distribution of HPeV CNS cases differed between the 2 study groups. In group 1, all the HPeV CNS cases were seen during the summer and early fall months (July -3, August -1, September -1 and October -4 cases). While in group 2, the dispersal was broader ranging from May to October (May -1, June -6, July -8, August -6 and October -1 case).

The clinical features, laboratory findings, treatment and outcomes of infants with HPeV CNS infection in group 1 and group 2 are presented in Table 1. The 2 groups were indistinguishable in terms of gestational age, age on admission, intensive care admission, clinical presentation and laboratory markers. Infants diagnosed with HPeV CNS infection in 2022 had a longer hospital stay (3 vs. 4 days, *P* 0.01) compared with group 1. The most common clinical sign was fever, followed by gastrointestinal symptoms, irritability/fussiness, altered level of responsiveness and rash, while respiratory problems occurred only in group 2. The serum C-reactive protein was significantly higher in group 2 (2 vs. 6.6 mg/L, *P* 0.01). The CSF analysis in both groups lacked any significant inflammatory response (ie, minimal pleocytosis). Among the infants who underwent a cranial ultrasound, [1/9 (1.1%) in group 1 and 3/22 (13.6%) in group 2], none of them had abnormal findings. On the contrary, abnormal brain magnetic resonance imaging (MRI) findings were detected in all the infants in group 1 who had an MRI performed (3/3) and in one-third (5/15) of the patients in group 2 (*P* 0.07). The most prevalent imaging finding was the restricted diffusion in the frontoparietal white matter and the corpus callosum. Resolution of the restricted diffusion areas was noted at 2

weeks and 4 months in 2 patients that had repeat brain MRI. Antibiotics were initially prescribed in most patients in both groups (89% vs. 95.5%, *P* 0.5). Thirty-two percent (7/22) of patients in group 2 received intravenous immunoglobulin (IVIG), whereas none of the patients in group 1 received treatment.

Almost half the infants in each group required intensive care unit (ICU) admission, though there were no deaths in either cohort. Among the infants who had follow-up in our system, 22% in group 1 and 27% in group 2 had documented neurodevelopmental complications including delays in motor skills or hypotonia requiring physiotherapy.

DISCUSSION

Our institution experienced a notable increase in infants with HPeV CNS infections between May and October 2022 using the same assay and clinical testing algorithm as the years prior. A sharp increase was observed starting May 2022 with a peak of 22 cases. These numbers reflect a significant increase in HPeV CNS cases in comparison to the same time periods in 2021 (1 case), 2020 (0 cases) and 2019 (3 cases). Moreover, we noted the most cases during summer and fall and saw an interruption in the biannual cycle typically described in HPeV infections with no cases in 2020.[3] Although the differences in these long-term patterns are unclear, both viral and host factors probably may affect the virus circulation. A hypothesis is that the mitigation measures during the SARS-CoV-2 pandemic reduced overall exposure to and infections with HPeV, leading to decreased development of protective immunity in mothers, less passive transfer of potentially protective immunity to their infants, and a larger population of susceptible infants. The fluctuations and rebounds of respiratory infections in young infants as a result of the SARS-CoV-2 pandemic is a well-documented phenomenon.[4] Another possibility is the emergence of a more virulent genetic lineages. We were unable to compare the current circulating HPeV clones with the previous ones due to the retrospective nature of the study and the lack of population-based studies.

Infants in both groups had very similar symptoms and clinical courses. Interestingly, in most cases, the CSF glucose and protein were normal, with a relative lack of significant CSF pleocytosis as it has been described elsewhere.[5] The presentation of these cases was similar to that described in clusters seen in the United Kingdom (106 cases), Tennessee (23 cases) and Australia.[5–7]

The majority (78%) of infants in group 1 and 36% in group 2 have unknown long-term outcomes. Several reports describe adverse long-term neurodevelopmental outcomes in infants with abnormal brain MRI imaging, as such outpatient monitoring for late CNS sequalae from CNS HPeV infection should be considered.[8–10]

The current management of severe infections due to HPeV involves supportive care while there is a lot of speculation regarding the use of IVIG.[1] Our data show that infants who received IVIG tended to have a more severe clinical course (as reflected by their more extended hospital stay, increased likelihood to be admitted to the ICU and/or oxygen support). In addition, infants who received IVIG had to a lesser degree (33% vs. 100%, *P* 0.07) abnormal findings in their brain MRIs. The nature and the size of our study do not allow us to make firm conclusions regarding IVIG indications of use and its therapeutic impact; however, this can be further studied in multicenter, prospective studies.

HPeV should be considered in the differential diagnosis of young infants presenting with fever, sepsis-like symptoms or meningitis, even with no laboratory findings of significant inflammatory response. The routine implementation of the meningitis/encephalitis multiplex panel allowed the identification of these young infants that previously would have not been diagnosed with meningitis and referred for neurodevelopmental follow-up. Nationwide epidemiologic studies are necessary to elucidate the dynamics of HPeV infections and inform public health authorities to optimize intervention strategies.

CONCLUSIONS

Our institution experienced a surge of HPeV CNS cases in young infants after lapsing of SARS-CoV-2 mitigation measures. Almost half of our patients required ICU admission, all had a favorable short-term outcome while the long-term prognosis remains elusive. Clinicians and public health authorities should be aware of the clinical presentation and epidemiological trends of HPeV infections. HPeV infections are not among the reportable diseases in the United States; however, surveillance may be helpful in designing preventive measures, defining better treatment strategies and implementing longitudinal multidisciplinary follow-up given the potential for neurodevelopmental sequelae.

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