Human Parechovirus Infection in an Infant Presenting with Hyperferritinemia

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ABSTRACT

Introduction: Human parechovirus (HPeV) is recognized as a cause of severe infections in infants.

Case Presentation: A 4-week-old febrile female with HPeV infection presented with persistent fevers and hyperferritinemia with normal C-reactive protein, suggestive of cytokine storm syndrome.

Discussion: HPeV is known to cause encephalitis, hepatitis, sepsis, and organ dysfunction. However, few have documented hyperferritinemia and the role of cytokines in disease progression and the role of intravenous immunoglobulins (IVIG) used in the treatment of HPeV-induced hyperinflammation/cytokine storm.

Conclusions: HPeV infections in infants can present with hyperinflammation and sepsis-like syndrome. IVIG may have a role in the treatment of severe parechoviral infections in children who present with hyperferritinemia.

INTRODUCTION

Human parechovirus (HPeV) is a single-stranded RNA virus belonging to the Picornaviridae family.[1] HPeV-1 is the most common type and is associated with mild gastrointestinal illnesses and respiratory tract infections in children. HPeV-3 is less common and linked with severe diseases, including sepsis and meningoencephalitis.[1] Recently, HPeV has been recognized as a cause of severe viral infections presenting with encephalitis, hepatitis, sepsis, neurological impairments, and organ dysfunction – especially in neonates and young infants.[1] Furthermore, there have been findings to suggest cytokine storm may contribute to more severe HPeV infections.[2] Here we report a case of an infant infected by HPeV who presented with persistent fevers, transaminitis, and hyperferritinemia who was treated with intravenous immunoglobulin (IVIG) and subsequently had a remarkable improvement in clinical symptoms and laboratory values.

CASE PRESENTATION

The patient is a 4-week-old female born at 37 weeks 6 days with a birth history complicated by marginal cord insertion and Group B streptococcal infection in the mother, which was adequately treated prenatally. She was brought to the pediatrician with primary concerns consisting of fussiness, reduced oral intake, emesis, and a rectal temperature of 100.1 °F. At this visit, it was reported that prior to falling ill, she was exposed to her cousin, who had tested positive for parechovirus. Physical exam was unremarkable, COVID-19 test was negative, and she was discharged home.

The following day, the patient continued to have similar symptoms, with the addition of looking "stiff," so she was reevaluated and sent to the emergency department for further workup. There, her vitals demonstrated a pulse of 182 beats per minute, respiratory rate of 36, oxygen saturation of 98% on room air, and a rectal temperature of 102.6 °F. A broad workup was ordered, which included a complete blood cell count (CBC) with differential, comprehensive metabolic panel (CMP), C-reactive protein level (CRP), procalcitonin, urinalysis (UA) with culture, blood culture, respiratory polymerase chain reaction (PCR) panel, and cerebrospinal fluid (CSF) studies. Her labs were significant for white blood cell (WBC) 4.6 x 103 /uL (7.0-20.0 x 103 /uL) with 34% lymphocytes and 11% (0%-11%) bands, sodium 130 mmol/L (136-

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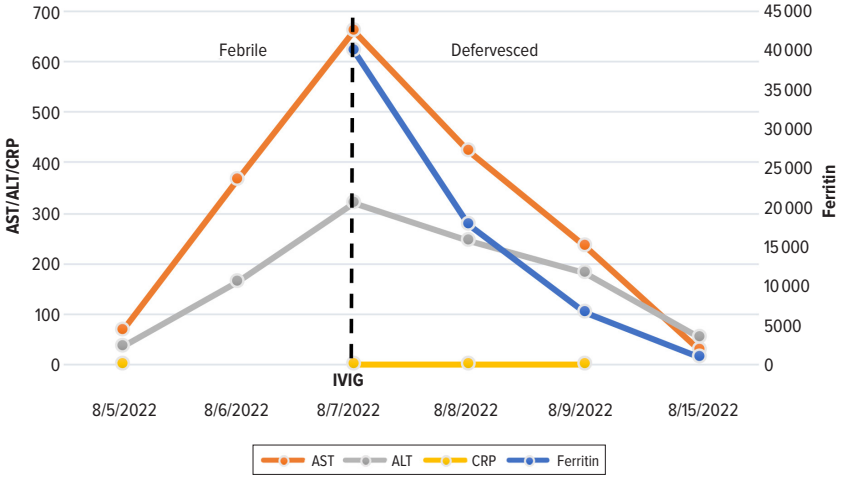
145 mmol/L), aspartate aminotransferase (AST) 69 U/L (15-60 U/L), alanine aminotransferase (ALT) 35 U/L (13-45 U/L), CRP < 0.29 mg/dL (< 0.31 mg/dL), procalcitonin of 0.41 ng/mL (< 0.50 ng/mL), unremarkable UA, negative respiratory PCR, blood-tinged CSF with few WBCs, positive CSF PCR for human parechovirus, normal CSF glucose, and normal CSF protein. The patient was transferred to the pediatric intensive care unit (PICU) for observation and further evaluation with pending blood and urine cultures.

In the PICU, she was started on IV fluids, antipyretics, famotidine, and ondansetron. Empiric antimicrobials were not started because laboratory findings were suggestive of viral etiology (parechovirus) for the febrile illness. On the second day of admission, she remained febrile, and her transaminases continued to rise with ALT climbing above the reference range to 164 U/L (AST 367 U/L). Her CBC was without leukocytosis, differential had 72% lymphocytes, blood cultures resulted negative, and she was started on continuous electroencephalogram monitoring to rule out seizures. Hyponatremia resolved on the second day of illness, and she did not have any clinical signs of dehydration. Given her status, the plan was to monitor liver function tests (LFT) daily.

On the third day of admission and due to persistent fevers, we suspected hyperinflammation secondary to parechoviral infection and checked a ferritin level. The repeated labs were notable for increased transaminases (AST 662 U/L, ALT 318 U/L) ferritin of > 40 000 ng/mL (200.0-600.0 ng/mL) and a CRP < 0.29 mg/dL. We hypothesized the parechoviral infection triggered an inflammatory hepatic process, likely producing clinical and diagnostic evidence of hyperinflammation/cytokine storm. IVIG 2g/kg (Octagam 10%) was administered over 6 hours.

Additionally, an echocardiogram and electrocardiogram were ordered to rule out cardiac involvement. These tests showed no acute cardiac pathology, but there was a non-hemodynamically significant patent foramen ovale with small left-to-right shunting. The patient defervesced immediately after IVIG administration and had improved oral intake. Laboratory values were trending down (AST 423 U/L, ALT 244 U/L, ferritin 17818 ng/mL, differential 65% lymphocytes with no bands) with a normal international normalized ratio and CRP. IV fluids were stopped, and pediatrics infectious disease was consulted; they felt supportive care was appropriate. On day 5 of admission, the patient remained afebrile, and laboratory values were reassuring. She was discharged and scheduled for a 1-week follow-up with her pediatrician for reevaluation and lab work. On discharge, notable labs included a WBC of 9.5 x 103 /uL, AST of 236 U/L, ALT of 180 U/L, and ferritin of 6707 ng/mL. At her 1-week follow-up, notable labs included a WBC of 14.7 x 103 /uL, AST of 30 U/L, ALT of 53 U/L, and a ferritin of 907 ng/mL (Figure).

Figure. Laboratory Values



Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

DISCUSSION

HPeVs are common childhood pathogens that predominantly cause mild infections in children between 6 months to 5 years of age. In children less than 3 months of age, HPeV can cause severe sepsis-like illness, meningitis, and hepatitis.[3] Our patient presented with sepsis-like illness with high fevers, decreased oral intake, emesis, and elevated transaminases and subsequently was found to have a markedly high ferritin value of > 40 000 ng/ml – levels that have not been well-documented in prior cases.[4]

There have been reports of neonates with severe HPeV infections presenting with hemophagocytic lymphohistiocytosis (HLH)-like illness with hyperferritinemia, cytokinemia, and cytopenia treated with corticosteroids and cyclosporine.[5] It is not well understood why HPeV triggers hyperinflammation in some infants. It is possible that immune pathways activated with HPeV are different from other viruses given multiple reports of children presenting with normal CRP and elevated serum ferritin, which was similarly observed in our patient. Serum ferritin has been studied extensively by immunologists. It is a known marker of inflammation and serves to enhance the immune system response. Ferritin is associated with inflammation as it is released from macrophages during infection and induces pro-inflammatory cytokines and immunosuppression, causing a positive feedback loop of inflammation via TLR-9 stimulation and activation of macrophage inflammasomes resulting in increased ferritin.[6] Elevated serum ferritin can cause uncontrolled inflammation with positive feedback loop resulting in tissue damage and increased morbidity and mortality in patients.[6]

The mechanism of HPeV induced-hyperferritinemia is unclear. It is possible that elevated serum ferritin levels could be a result of viral or immune-mediated hepatitis. Ferritin is stored in the liver cells and may leak out into the blood due to the damage caused by the virus.[6] Elevated serum ferritin known to fuel inflammation could cause cytokine storm via positive feedback loop triggered by elevated ferritin. While a cytokine panel would have been useful in understanding the cytokine response in our patient, we were limited by timely availability of results, and it would have incurred unnecessary costs and ultimately not changed the course of treatment at that point in time.

There are multiple reports of HPeV-induced cytokine storm. The largest known cohort of 118 infants infected with HPeV was reported from Australia in 2015. Two children in that cohort had hemophagocytic lymphohistiocytosis (HLH) or Kawasaki disease-like illness. One child received IVIG and defervesced; the other child recovered without any immunomodulatory therapy.[7] Another case report showed elevated cytokine levels (MCP-1, IL-6, IL-10, IFN-γ, and TNF-α) in 2 HPeV-3 infected infants, suggesting the role of cytokine storm in the pathophysiology of parechoviral infection.[2] Our 4-week-old patient met criteria for systemic inflammatory response syndrome with an elevated core temperature above >38.5°C and a depressed leukocyte count for the patient's age. Additionally, elevated transaminases and extremely elevated ferritin levels with normal CRP supported the idea of HPeV-induced hyperinflammation as the cause of her illness.[8] The clinical decision was made to administer a single, high dose of IVIG.

Prior experience of using IVIG to treat hyperinflammation is primarily in Kawasaki disease and more recently in treating COVID-19-associated multisystem inflammatory syndrome in children (MIS-C). IVIG had been used alone as well as in combination with other therapies for cases of viral encephalitis in the pediatric population – primarily for enterovirus, parvovirus, and mumps.[9,10] IVIG is currently the recommended first-line treatment for Kawasaki disease due to its anti-inflammatory effects, which subsequently reduces myocarditis and arterial abnormalities in treated patients.[11] IVIG has been successful in treating MIS-C, a clinical syndrome of children with a history of SARS-CoV-2 infection, which is followed by systemic inflammation, fever, and multiorgan dysfunction.[12] IVIG has been used to neutralize a select strain of parechovirus in vitro and in supportive therapy for encephalitis in prior case reports.[13] Despite each of these prior documented uses for IVIG, our literature review did not reveal any reported parechoviral-induced cases of viral hepatitis in infants associated with hyperferritinemia that had been treated specifically with IVIG.

Without prior literature to base treatment selection on, IVIG was chosen as the treatment for this infant given our suspicion for cytokine storm syndrome and the similarities of the patient's clinical presentation with other inflammatory diseases for which IVIG has been used – particularly Kawasaki disease and MIS-C. Ultimately, the strong association between the time of administration of IVIG and the stark decrease in ferritin levels, LFTs, and defervescence suggests IVIG may be considered for treatment of parechovirus-induced viral hepatitis presenting with hyperferritinemia. Importantly, this patient's LFTs and ferritin levels remained low at her follow-up appointment, and she was doing well clinically 1 week after discharge. It is important to note that laboratory and clinical improvement may have been seen without the use of IVIG; however, given the worsening clinical symptoms and similarities of the case to Kawasaki and MIS-C patients successfully treated with IVIG, we felt it was an appropriate intervention for our patient. The dosage of IVIG was based upon the treatment of hyperinflammation states such as Kawasaki and MIS-C, which is 1 dose followed by observation for a response and a second dose if not improved. Our patient improved with a single dose.

The administration of IVIG does not come without risks, which need to be considered for each patient. Given that it is a blood transfusion, there is the risk of an adverse reaction or even anaphylaxis. Infection is also a risk that is not negligible. Furthermore, for children who receive IVIG, it is recommended that they do not get any live vaccines for a year after. This would postpone administration of the MMR vaccine as well as others that could increase risk of exposure to additional viruses.

Our patient was discharged on day 5 of admission, while some infants treated with antibiotics alone were discharged 6 to 8 days after admission.[1,2] Although 1 infant with a suspected severe systemic inflammatory response was treated with IVIG and was first discharged on day 8 of admission, it is important to note IVIG was not administered until day 5 of admission. Retrospectively, our hypothesis would support the idea that had IVIG been administered sooner, it is possible this infant may have been discharged earlier.[14]

One limitation of this study is that a cytokine panel was not collected to confirm the cytokine storm. This was not deemed necessary as the patient defervesced and had remarkable improvement. However, if she was not responsive or if her condition was worsening, a cytokine panel would have been ordered, and other therapies, such as steroids, anakinra (an interleukin-1 antagonist), plasma exchange, and interleukin-6 antagonists would have been potential next steps. Furthermore, it would be of interest to see which cytokines are elevated and perhaps an additional target for future therapeutics. Another limitation was that we did not obtain titers of neutralizing antibodies against HPeV before and after IVIG administration; future studies or clinical cases would likely benefit from such measurement to better understand the potential mechanism of IVIG.

CONCLUSIONS

In children with HPeV infection presenting with persistent fever and hepatitis, a check of serum ferritin level might help assess if

the patient has HPeV-induced hyperinflammation. Currently, there is not enough evidence to recommend IVIG as a treatment for HPeV-induced hyperferritinemia. IVIG use must be based on the best clinical judgement after weighing its risks and benefits.

Funding/Support: None declared.

Financial Disclosures: None declared.

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