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Human Parechovirus and Enterovirus Initiate Divergent Innate Immune Responses in the CNS: Pathogenic and Diagnostic Implications

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BACKGROUND

The picornaviruses human parechovirus (HPeV) and enterovirus (EV) cause a wide range of diseases, including CNS infections, which can be severe and potentially fatal. EV causes most cases of pediatric meningoencephalitis worldwide, and HPeV type 3 (HPeV3) is the most common cause of viral meningitis in young infants. Each year in the United States, there are over 75,000 cases of aseptic meningitis. Despite reassuring short-term outcomes, negative neurodevelopmental sequelae are increasingly associated with HPeV and EV.

The pathogenesis and severity of HPeV and EV infections are undoubtedly linked to the innate and adaptive immune responses elicited by these viruses. Until this work, the innate immune response mounted against HPeV was largely unknown. Pattern recognition receptors in the CNS, including a number of Toll-like receptors located in different cells and subcellular compartments, detect invading pathogens and cause the release of cytokines and chemokines almost immediately into the CSF compartment at measurable levels. Essentially, this allows for determination of an amplified, infectious agent-specific pattern.

These virus specific patterns of innate immune activation may provide insight into the pathogenesis of the corresponding disease states. Also, since these infections have similar clinical presentations, the immune profiles may be useful for rapid pathogen diagnosis in the clinical setting.

OBJECTIVES

1. Quantify and characterize the innate immune cytokine/chemokine responses to HPeV and EV infections.
2. Compare and contrast CSF cytokines and chemokines levels produced in HPeV CNS infections to those produced in response to EV CNS infections.
3. Identify patterns of innate immune activation caused by HPeV and EV to gain insight into the pathogenesis of these two common picornaviruses.
4. Determine if CSF cytokine/chemokine profiles are potentially useful for rapid identification of CNS viral infections in clinical situations.

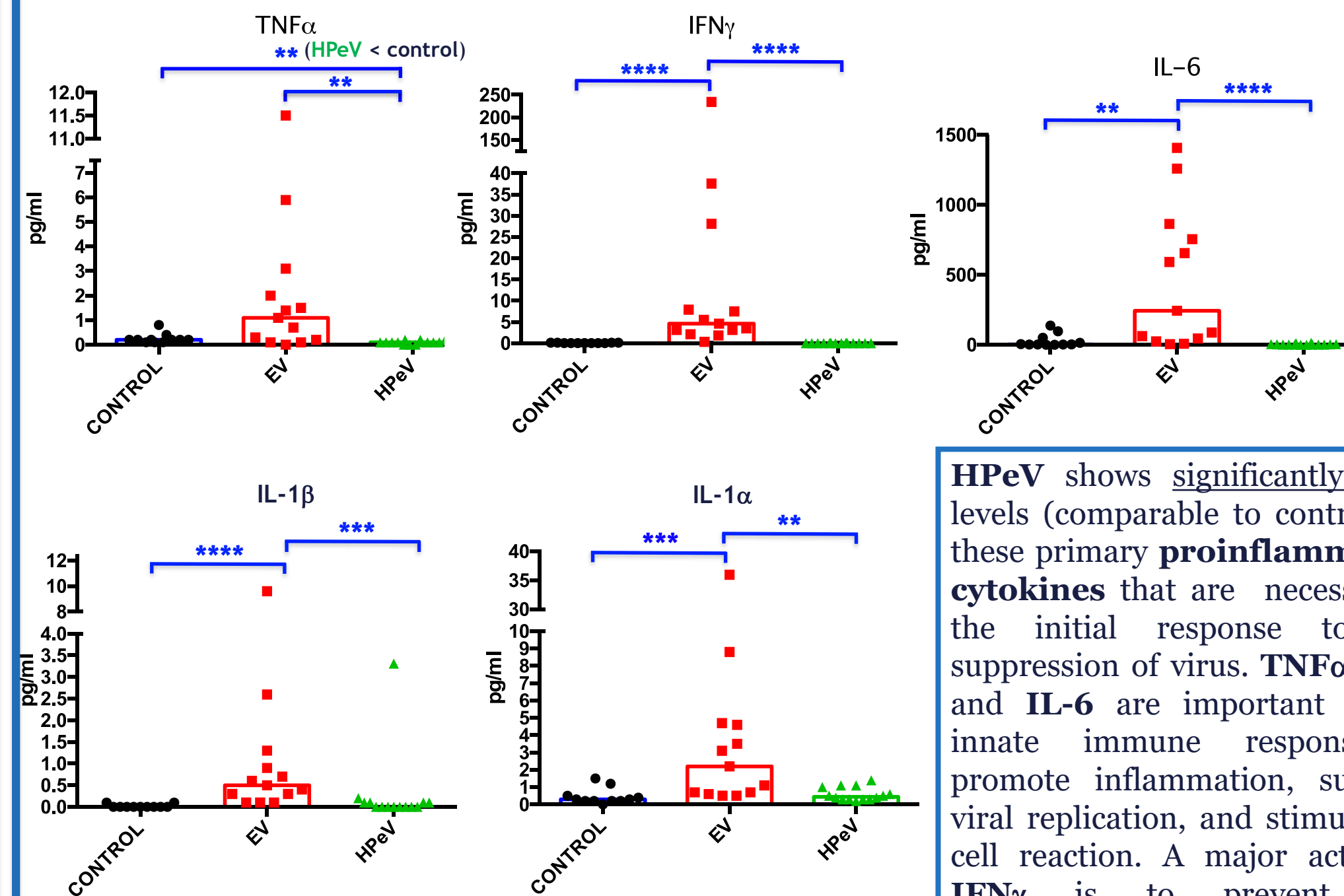
STUDY DESIGN

CSF samples from patients with HPeV and EV meningitis and patients negative for CNS infection (Controls) were analyzed to determine levels of cytokines and the chemokine IP-10 (CXCL10). The "control" group includes CSF samples from patients in which CNS infection was excluded via microbiological/molecular testing. These "control" cases include: febrile seizures from rhinovirus and adenovirus systemic infection, E. coli UTI, choroid plexus papilloma, medication/toxin ingestion, pneumonia, and altered mental status.

A multiplex sandwich enzyme-linked immunosorbent assay (ELISA) was used to determine CSF levels of IFN γ , IL-1 α , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, TNF α , in CSF samples. A fluorescent bead-based ELISA assay system was used to determine CSF levels of IP-10/CXCL10 and IL-15

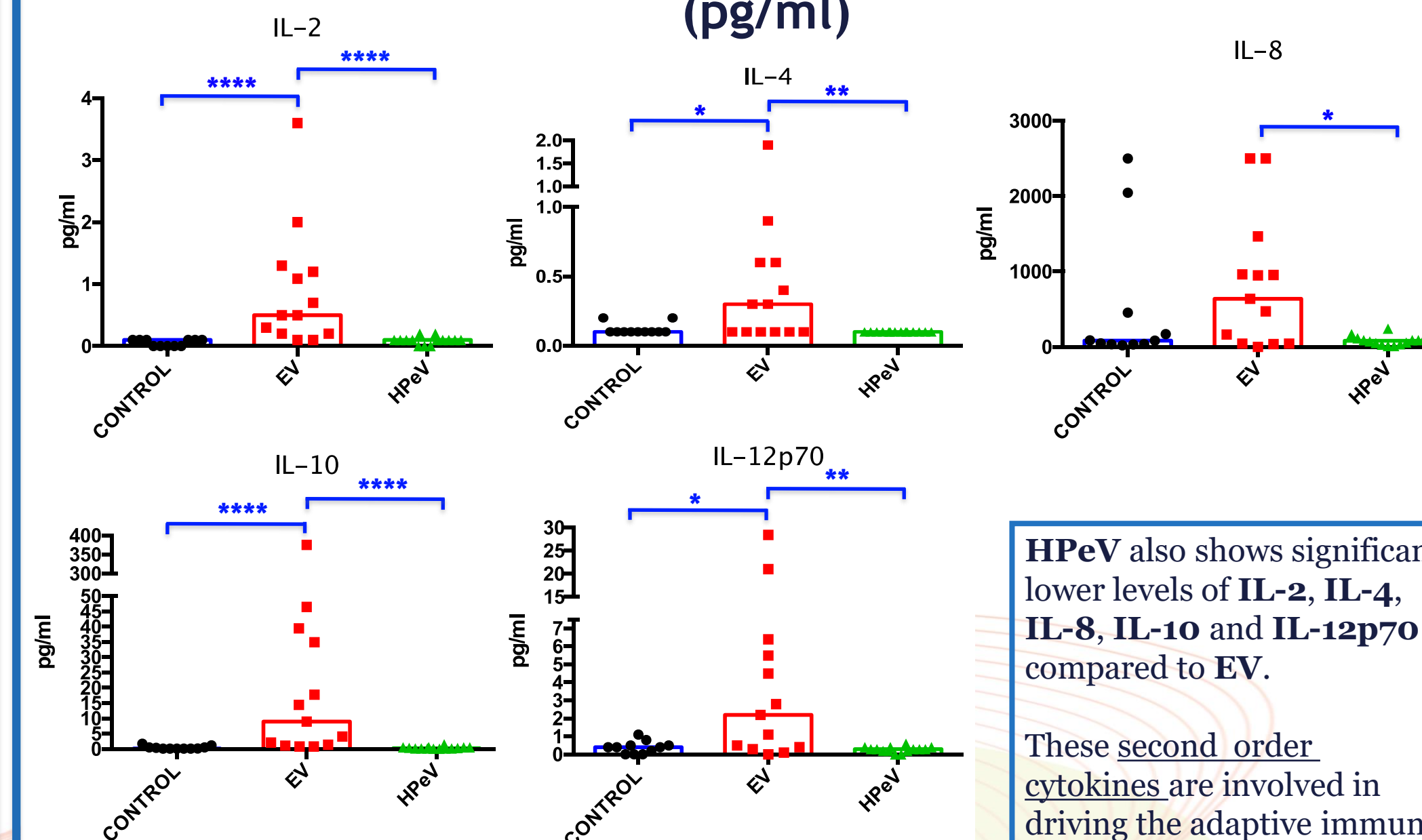
RESULTS

Levels of primary proinflammatory cytokines (pg/ml)



HPeV shows significantly lower levels (comparable to controls) of these primary **proinflammatory cytokines** that are necessary in the initial response to and suppression of virus. TNF α , IL-1, and IL-6 are important in the innate immune response to promote inflammation, suppress viral replication, and stimulate T-cell reaction. A major action of IFN γ is to prevent viral replication.

Levels of cytokines involved in priming adaptive immunity (pg/ml)



HPeV also shows significantly lower levels of IL-2, IL-4, IL-8, IL-10 and IL-12p70 compared to EV.

These second order cytokines are involved in driving the adaptive immune response against viral infection and dampening of inflammation.

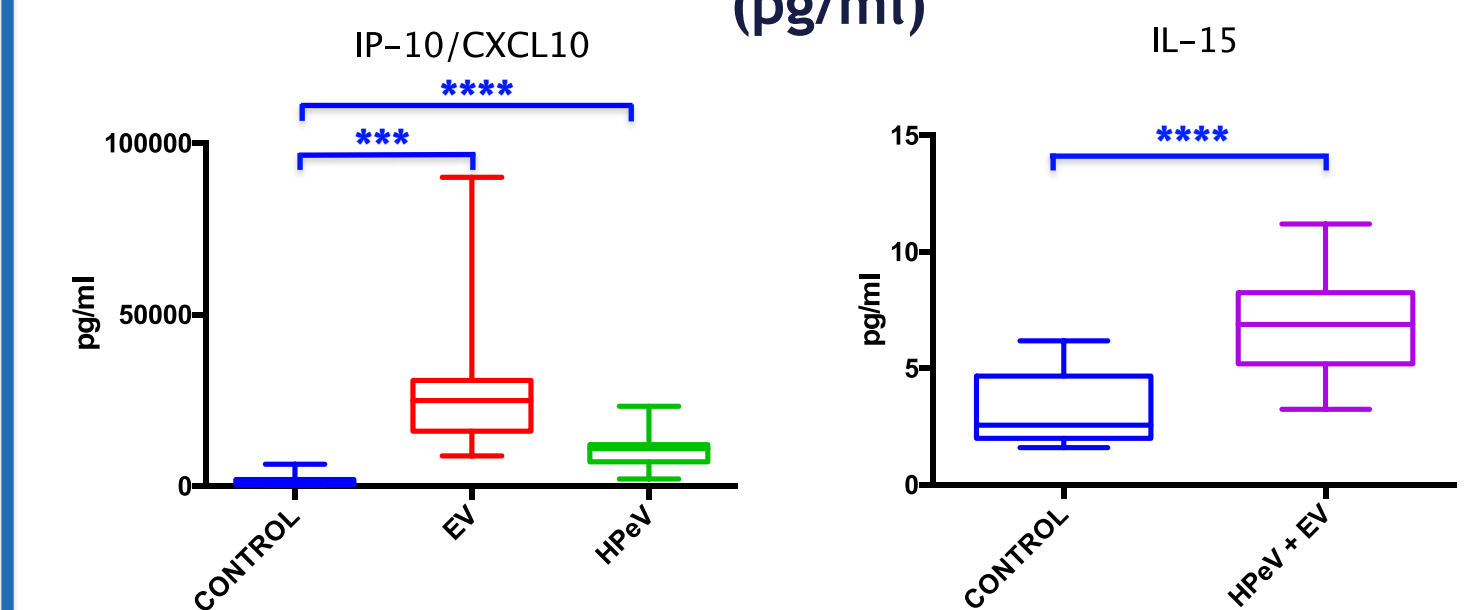
Statistical significance was evaluated by nonparametric t-test (Mann-Whitney test). Number of asterisks = p value strength

RESULTS

Clinical data table

Clinical Group	CSF negative	EV meningitis	HPeV meningitis
Male	36%	46%	64%
Age (years)	3.0 + 4.0	4.1 + 5.2	1.3 + 4.5
Temp max (°F)	101.0 + 1.6	102.2 + 1.1	101.8 + 1.9
Length of Stay	2.5 + 1.2	1.4 + 0.5	3.2 + 1.5
CSF WBC (cells/ul)	2.5 + 2.9	2083 + 4010	39.2 + 86.9
CSF glucose (mg/dl)	60.6 + 15.1	52.1 + 15.3	45.9 + 7.1
CSF protein (mg/dl)	27.6 + 10.8	288.3 + 477.4	80.42 + 78.9
Viral PCR Ct	N/A	35.2 + 2.3	37.2 + 1.6
Seizures	27%	8%	0%
Long term sequelae	N/A	0%	7%

Innate Immune markers suggest viral infection (pg/ml)



Elevation of the immune markers IP-10 (CXCL10) and IL-15 in HPeV compared to control group distinguishes HPeV from non-infectious states. Additionally, elevation of IL-15 HPeV and EV is suggestive of a viral infection.

SIGNIFICANCE/CONCLUSIONS

- HPeV CNS infection elicits a markedly different innate immune cytokine response than EV.
- Since HPeV and EV infections have a similar clinical presentation, the cause of the distinct immune responses is not attributable to different severity of disease state.
- HPeV appears to evade the innate immune system with most notable deficiencies in the signals which prime the adaptive immune system (ex: differentiation of CD4 T-cells and antibody production). This phenomenon may lead to persistent infection and the long-term sequelae associated with HPeV infection.
- Elevated IP-10 and IL-15 serve as reliable indicators of CNS infection regardless of initial CSF cell counts and labs. Elevated IL15 further supports a viral etiology.