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Acquired Hemophagocytic Lymphohistiocytosis: a Case Report of Two Neonates

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Abstract

We report two cases of Herpes Simplex Virus (HSV) induced hemophagocytic lymphohistiocytosis (HLH). These cases highlight that neonates with HSV may have concurrent secondary HLH, a life threatening condition in which prompt diagnosis and treatment can drastically improve survival. Therefore, a low index of suspicion is needed to send, cost effective, sensitive screening blood tests for HLH in critically ill neonates with viral infections. Ferritin is especially useful as a diagnostic tool.

Keywords: HLH, Herpes Simplex Virus, HSV, Ferritin

Introduction

The fundamental principal behind most diagnostic evaluations is to find a single unifying cause of a patient's presenting symptoms. This principal may delay diagnosis and management when two simultaneous disease processes coexist. We report two cases of HSV induced HLH, emphasizing the importance of considering the prospect of two interrelated, yet distinct diseases, when presented with an infant in multisystem organ failure. We also highlight the importance of obtaining a *ferritin level* in infants with multisystem organ failure of unknown etiology. A ferritin level is an invaluable diagnostic tool in evaluation and may alter treatment decisions.

Case Presentation

First case

A 2905g term female was born by vaginal delivery (SVD), with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The pregnancy was unremarkable except for Group B Strep (GBS) colonization (inadequate perinatal treatment) and a prior history of HSV-1 infection (detectable

IgG levels), but no active lesions at delivery. The infant was discharged on day of life (DOL) 2. On DOL 7 the infant presented to an emergency department with lethargy and decreased oral intake. She was noted to be hypoglycemic, hypothermic, and in respiratory distress requiring nasal cannula oxygen during a sepsis evaluation. Within 24 hours she rapidly progressed to multisystem organ failure: cardiovascular and respiratory instability requiring vasopressors and intubation. Ultimately, she developed anuric renal failure, liver failure with severe coagulopathy, and cytopenia of all three cell lines. The infant was transferred to a Level IV neonatal intensive care unit (NICU) where she deteriorated rapidly. An elevated ferritin level of 234 000 μg/L, neutropenia, thrombocytopenia, anemia, hypofibrinogenemia, hemophagocytosis, and low NK cell activity led to a diagnosis of hemophagocytic lymphohistiocytosis (HLH). Prior to treatment with dexamethasone and etoposide, the infant's blood HSV PCR resulted positive for HSV-1. Her diagnosis was refined to HSV induced HLH. After extensive discussion with the family, the decision was made to continue treatment of HLH (and disseminated HSV). Despite treatment, her conditioned worsened, and she died on DOL 11.

Second case

A 3400g term female was born via SVD, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The pregnancy was unremarkable except for GBS colonization (inadequate perinatal treatment), without history of maternal HSV. She underwent a 48 hour septic evaluation for maternal chorioamnionitis and was discharged home on DOL 2. Subsequently, she presented to an emergency department on DOL 12 for lethargy, decreased oral intake, and emesis. She was noted to be hypothermic, and underwent a septic workup. Within 24 hours she developed multisystem organ failure. Her clinical status deteriorated, requiring intubation and transfer to a level IV NICU for ongoing vasopressor support. An elevated ferritin level of 95 000 ng/mL μg/L, neutropenia, anemia, thrombocytopenia, hypertriglyceridemia, hypofibrinogenemia, elevated soluble IL-2, and low NK cell activity met the diagnostic criteria for HLH. Shortly thereafter, she was found to have disseminated HSV-2 (positive blood PCR), and her diagnosis was refined to HSV induced HLH. Treatment proceeded for both HLH and disseminated HSV, and on DOL 22 she died from multisystem organ failure despite maximal treatment.

Discussion

Hemophagocytic lymphohistiocytosis is a rare disease characterized by an uncontrolled systemic inflammatory response.[1-3] Natural Killer (NK) cells are part of the innate immune system and play an important role in both activating the immune system in response to an infection and suppressing the immune system when the infection has been eliminated.[3] In HLH, NK cells are unable to eliminate the infected cell or suppress activated components of the innate immune system. This results in the persistent activation of the inflammatory cascade and an uncontrolled systemic inflammatory syndrome.[2]

Diagnosis of HLH is often delayed or never considered because the symptoms are nonspecific. [2,4] The diagnosis can be established either with known genetic mutations or when five of the eight diagnostic criteria are fulfilled (Table 1).[2, 3, 5] As demonstrated in this report, the ferritin level may be crucial in the diagnosis of HLH. Ferritin is an inflammatory marker that is not routinely obtained in the NICU.[1,4] Ferritin is an acute phase reactant and can be elevated in a number of inflammatory conditions. However the degree of elevation provides insight to the underlying cause of multisystem organ failure in an infant. A ferritin level in the high hundreds to low thousands may be seen in gestational alloimmune liver disease, whereas a ferritin level in the thousands suggest a diagnosis of HLH. In contrast, a ferritin level <500 ug/L is more consistent with an acute bacterial or viral infection.

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Allen et al. published a retrospective review demonstrating that admission and peak ferritin levels greater than 10,000 ug/L are highly suggestive of HLH, with a sensitivity of 90% (95% CI 71-100) and specificity of 96% (95% CI 94-98) (Table 2).[4] This corresponds to a positive predictive value of 41% and negative predictive value of 99.7% when an admission peak ferritin level greater than 10,000 ug/L is present.[4]

Additionally, once a diagnosis of HLH is made, ferritin levels can be used as a prognostic variable. Lin et al. demonstrated that patients with ferritin levels greater than 11,000 μg/L during the first three weeks of treatment had an increased risk of mortality (OR 5.6) and that a rapid fall in ferritin levels following therapy initiation was associated with decreased mortality (<50% ferritin decrease versus >96% ferritin decrease, OR 17.42).[1]

The diagnosis can be established if one of either 1 or 2 below is fulfilled

(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of t he eigfht criteria below)

(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
- Fever
- Splenomegaly
- Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood.
- Hemoglobin < 90g/L in infants < 4 weeks:Hemoglobin <100g/L)
- Platelets < 100 × 10^9/L
- Neutrophils < 1.0 × 10^9/L
- Hypertriglyceridemia and/or hypofibrinogenemia:
  - Fasting triglycerides ≥ 3.0 mmol/L(i.e., ≥ 265 mg/dl)
  - Fibrinogen ≤ 1.5 g/L
- Hempphagocytosis in bone marrow or spleen or lymph nodes
- No evidence of malignancy

(B) New Diagnostic criteria
- Low or absent NK-cell activity (according to local laboratory reference)
- Ferritin ≥500 μg/L
- Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml

Table. 01 *Diagnosis guidelines for HLH. Adapted with permission from Henter et al.[5]*

There are limited reports of neonatal HSV induced HLH in the literature. In 2008, Yamada et al. reported a case of HSV-1 induced HLH in an infant that clinically improved after initiation of HSV and HLH treatments.6 Suzuki et al. published a nationwide survey of identified neonatal HLH cases occurring in Japan over a 10 year period, between 1997 and 2007. Of the 20 HLH cases , the overall survival was 40% (8 of 20). Of the 6 HSV induced HLH cases, the survival was 33% (2 of 6). Survival of familial HLH was 29% (2 of 7), and survival of other (cytomegalovirus, coxsackievirus, unidentified) was 57% (4 of 7).[7] Although there is a high mortality in infants with HLH, prompt diagnosis and treatment improves the chance of survival.

This case report demonstrates that both diagnosis and management of HLH can be complicated by the concurrent diagnosis of HSV. Like HLH, the diagnosis of HSV can be difficult, because the initial presentation is often nonspecific. Sazuki et al. found that HSV induced HLH trended towards worse outcomes when compared with other secondary forms of HLH.[7] However, prompt diagnosis and treatment of concurrent, secondary HLH can improve survival. The treatment of HLH is dictated by the HLH-94 protocol. This protocol includes the immunosuppressive drugs dexamethasone, etoposide, methotrexate, and cyclosporine.[3] Major side effects of HLH treatment include immunosuppression, bone marrow suppression, and hypotension.[3] It may seem counterintuitive to treat HLH in the setting of an active HSV infection, where hypotension and pancytopenia may already be present, and where immunosuppression may limit the ability to treat the viral infection. However, without early treatment of HLH and the associated uncontrolled cytokine release, isolated treatment of HSV is thought to significantly decrease survival. Early treatment with acyclovir and the HLH-94 protocol has been shown to improve mortality.[3,5,6] After expert hematologic consultation, it was decided for both presented cases, that despite the risk, both HSV and HLH should be concurrently treated.

Maximum ferritin level (µg/L)	Other variable	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Number of Patients
3,000		90%(71-100)	77%(73-82)	11%(4-18)	99.6%(99-100)	330
6,000		90%(71-100)	90%(71-100)	21%(9-34)	99.7%(99-100)	330
10,000		90%(71-100)	96%(94-98)	41%(20-61)	99.7%(99-100)	330
10,000	LDH > 4,000 µ/L	86%(60-100)	98%(94-100)	75%(45-100)	98.8%(96-100)	92
10,000	Fever	90%(71-100)	98%(96-99)	56%(32-81)	99.7%(99-100)	329
10,000	ALT >100 µ/L	70%(42-98)	97%(94-99)	47%(21-72)	98.7%(97-100)	242
10,000	AST > 300 µ/L	70%(42-98)	98%(96-100)	58%(30-86)	98.7%(97-100)	241
10,000	Cytopenia (2 or 3 lines)	40%(10-70)	98%(97-100)	44%(12-77)	98.1%(97-100)	322
10,000	Splenomegaly	50%(19-81)	99%(98-100)	56%(23-88)	98.4%(97-100)	329

Table. 02 *Statistical analysis of HLH and peak ferritin levels. Adapted with permission from Allen et al.[4]*

Note: -Number of patients for different combinations of lab varies based on availability of lab values. Lab indicated in "other variable" were only included in analysis if they were obtained within 24 hr of ferritin.

In summary, we report two cases of HSV induced HLH to highlight that HLH as an often missed diagnosis in the setting of multisystem organ failure in an infant. An initial ferritin level can be an invaluable part of the initial work-up. Additionally, this case report stresses that two diagnoses may concurrently exist in one patient, and that the interaction of these disease processes may complicate the overall management of the patient.

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Abbreviations

GBS: Group B Streptococcus
DOL: Day of Life
HLH: Hemophagocytic Lymphohistiocytosis
HSV: Herpes Simplex Virus
NICU: Neonatal Intensive Care Unit
NK: Natural Killer
SVD: Spontaneous Vaginal Delivery

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