EDITORIAL

The HScore to Diagnose HLH in Scrub Typhus: Overdiagnosis or under Diagnosis and Does It Really Matter?

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Hemophagocytic lymphohistiocytosis (HLH) was first described by Farquhar and Claireaux in 1952 in two siblings who both succumbed to this devastating disease.[1] Hemophagocytic lymphohistiocytosis is a condition with potentially devastating consequences which is characterized by a greatly exaggerated inflammatory immune response and a cytokine storm which is activated by a genetic or acquired overactivation of the immune response.[2] Whereas the primary form of HLH (pHLH) is due to a genetic defect and is more common in children, secondary HLH (sHLH) is being increasingly diagnosed in adults. Secondary hemophagocytic lymphohistiocytosis is usually associated with infections, malignancies or autoimmune diseases (sHLH in patients with autoimmune conditions like SLE, still's disease, etc., is called macrophage activation syndrome).[3] The infections most commonly associated with sHLH are viral infections like EBV, CMV, HIV or influenza. More and more cases of sHLH following tropical infections are being reported however.[4,5]

While sHLH following Dengue constitute a majority of the cases of sHLH following tropical infections, instances of this dangerous complication are being increasingly recognized in the other tropical infections as well.

Suresh Selvam et al.[6] diagnosed sHLH in 28 of 150 patients admitted to their hospital with scrub typhus. They observed that the patients diagnosed with sHLH were much sicker on admission and had a greater need for mechanical ventilation and vasopressors. Serum Ferritin was the most reliable marker of HLH in this study. Of the patients diagnosed with HLH 21.4% died as against 6.6% deaths in those without HLH.

Suresh Selvam et al. used the HS score to diagnose HLH in their patients. Traditionally, the HLH 2004 criteria were used to diagnose HLH.[7,8] These criteria were never validated in adults and had some other limitations. The HS score was devised to overcome these limitations. Only 8 of the 28 patients diagnosed with HLH by the HS score in this study met the HLH 2004 criteria. It must also be noted that more than a third of the patients admitted with scrub typhus would have qualified for the diagnosis of HLH if the traditional cut off of 169 points on the HS score were used. A much higher cut-off score of 200 was used in this study, despite the fact that a majority of patients did not undergo a bone marrow examination (and thus lost 35 potential points on the HS score). Though this might have increased the specificity of the diagnosis, some of the cases in which people truly had HLH were probably underdiagnosed. The HS score (at least at the conventional cut-off) might not be very specific for the diagnosis of HLH in tropical infections because several of the abnormalities overlap. In fact, none of the patients included in the original study to validate the HS score suffered from a tropical infection. Though a couple of studies have subsequently validated the HS score in Adult critically ill patients, these studies were in countries where tropical infections are rare.[9,10] The HS score therefore needs to be validated in the setting of tropical infections, and a cut-off value that is more appropriate for tropical illnesses might need to be defined.

In any case, a clear definition of HLH is probably most relevant in research settings. A clinician merely needs guidance on how to identify those patients with a severe tropical infection who are likely to benefit from immunomodulation. Only 10 of the 28 patients (35%) diagnosed with HLH in this study received some form of immunomodulatory therapy. 6 of the 28 patients died. The authors haven't mentioned whether the mortality rates were different in those who received immunomodulation. Even if there was such a difference in mortality, many of the patients with HLH survived after receiving only antibiotics specific for scrub typhus. This is not entirely surprising because the most important step in the management of infection related HLH is to treat the primary infection.

Immunomodulation should be considered in patients with tropical infections, irrespective of their HS score, if they are rapidly deteriorating and especially if associated with high fever, cytopenia and very high ferritin levels. On the contrary, a high HS score or high Ferritin levels should not be an indication for immunomodulatory therapy in patients who are responding to infection specific therapy, irrespective of their HS score.[4,11]

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References

1. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. Arch Dis Child 1952;27(136):519–525. DOI: 10.1136/adc.27.136.519.
2. Lachmann G, La Rosee P, Schenk T, Brunkhorst FM, Spies C. Hemophagocytic lymphohistiocytosis: A diagnostic challenge on the ICU. Anaesthesist 2016;65(10):776–786. DOI: 10.1007/s00101-016-0216-x.
3. Canna SW, Behrens EM. Making sense of the cytokine storm: A conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am 2012;59(2):329–344. DOI: 10.1016/j.pcl.2012.03.002.
4. Rajagopala S, Singh N. Diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics: Systematic review from the Indian subcontinent. Acta Med Acad 2012;41(2):161–174. DOI: 10.5644/ama2006-124.49.
5. Kodan P, Chakrapani M, Shetty M, Pavan R, Bhat P. Hemophagocytic lymphohistiocytosis secondary to infections: A tropical experience! J Postgrad Med 2015;61(2):112–115. DOI: 10.4103/0022-3859.150904.
6. Selvam S, Tuli A, Yuvasai KP, Saini S, Erla SR, Kaur J, et al. Predicting secondary hemophagocytic lymphohistiocytosis in adult patients with scrub typhus and its prognostic significance. Indian J Crit Care Med 2024;28(9):823–831.
7. Henter JI, Horne AC, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(2):124–131. DOI: 10.1002/pbc.21039.
8. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive Hemophagocytic syndrome. Arthritis Rheumatol 2014;66(9):2613–2620. DOI: 10.1002/art.38690.
9. Knaak C, Nyvlt P, Schuster FS, Spies C, Heeren P, Schenk T, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. Crit Care 2020;24;24(1):244. DOI: 10.1186/s13054-020-02941-3.
10. Meena NK, Sinokrot O, Duggal A, Alpat D, Singh ZN, Coviello JM, et al. The performance of diagnostic criteria for hemophagocytic lymphohistiocytosis in critically ill patients. J Intensive Care Med 2020;35(12):1476–1482. DOI: 10.1177/0885066619837139.
11. Kan FK, Tan CC, Von Bahr Greenwood T, Khalid KE, Supramaniam P, Hed Myrberg I, et al. Dengue infection complicated by hemophagocytic lymphohistiocytosis: Experiences from 180 patients with severe dengue. Clin Infect Dis 2020;70(11):2247–2255. DOI: 10.1093/cid/ciz499.