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Title: INFLAMMATORY MARKERS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS - A SINGLE CENTRE STUDY

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Background:

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathological immune activation that can be difficult to distinguish from other cytokine storm syndromes such as Adult-Onset Still's disease (AOSD) and COVID-19 cytokine storm (CCS). The HLH-2004 criteria and HScore are the best available diagnostic criteria but have important limitations. Many of the tests included in the current HLH-2004 criteria, such as flow cytometry for NK cell cytotoxicity and cytokine analysis, are only available in specialized centers, and while useful in pediatric HLH, are less so in adult HLH which is characterized by hyperinflammation. Inflammatory markers such as ferritin, are not specific for HLH and can be seen in several hyperinflammatory syndromes.

We sought to examine the clinical utility of a simply, readily available inflammatory marker, C-reactive protein CRP) in combination with sIL2r levels in distinguishing HLH from two similar cytokine storm syndromes, AOSD and CCS.

Aims:

Our aim is to analyze patterns of elevation in CRP and sIL2r to help clinicians in the differential diagnosis of HLH, AOSD, and CCS.

Methods:

A retrospective chart review was conducted for 61 patients with secondary HLH, 10 patients with AOSD, and 13 patients with CCS. Demographic data as well as inflammatory biomarkers including CRP and sIL2r levels were collected if drawn within 72 hours of the acute episode that led to diagnosis, and prior to treatment. The Kruskal-Wallis test was used to compare CRP in the HLH, AOSD, and CCS groups, as well as to compare CRP in HLH subgroups by underlying trigger (infection, malignancy, autoimmune, and idiopathic). The Kruskal-Wallis test was also used to measure and compare sIL2r levels in the HLH group compared to AOSD, as well as by HLH subtype.

Results:

C-reactive protein is significantly lower in secondary HLH (*Mdn* = 76.4) compared to AOSD (*Mdn* = 114.5, p = 0.039) and CCS (*Mdn* = 121.0, p = 0.003). When analyzed by subtype, CRP levels in malignancy-associated HLH (MAHS) were not significantly different than AOSD or CCS, while CRP levels were significantly lower in the non-MAHS groups (*Mdn* = 58.9, p = 0.01) compared to AOSD and CCS (p <0.001), particularly when compared to infection-associated HLH (IAHS) (*Mdn* = 32.7, p = 0.009). Soluble IL2 receptor levels were significantly higher in the HLH group (*Mdn* = 7436.0, p = 0.03) compared to AOSD (*Mdn* = 2252.0).

Summary/Conclusion:

C-reactive protein is significantly lower in HLH compared to AOSD and CCS, specifically in non-MAHS, and may be a useful and easily accessible biomarker aiding in the differential diagnosis of HLH. Soluble IL2 receptor levels are a useful biomarker in distinguishing AOSD from HLH, as it is not as significantly elevated in AOSD.

Keywords: Macrophage, Inflammation, IL-6, Cytokine