Acute Necrotizing Encephalopathy of Childhood and Central Nervous System Haemophagocytic lymphohistiocytosis: Two faces of the same coin

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INTRODUCTION

- Haemophagocytic lymphohistiocytosis (HLH) and acute necrotizing encephalopathy of childhood (ANEC) are life-threatening conditions with severe consequences and high mortality.

- HLH – a syndrome with severe systemic hyper-inflammation with characteristic features of unremitting fever, cytopaenias, hepatosplenomegaly and elevation of typical HLH biomarkers.

- High mortality rate → prompt recognition and treatment essential.

- Systemic HLH is well known, CNS HLH is not.

- ANEC - a type of acute infectious encephalopathy, characterized by a rapid decline in consciousness after a non-specific febrile viral illness and seizures.

- Although both are life-threatening diseases, the association of these diseases has been rarely observed.

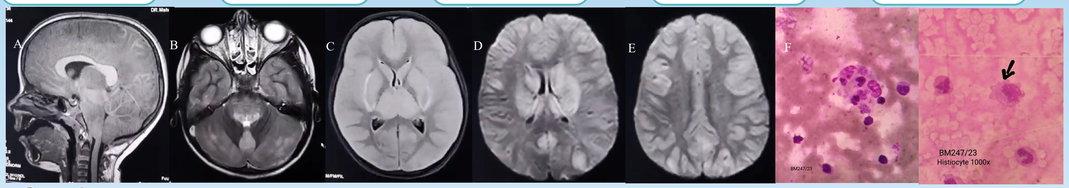
PATHOGENESIS

In HLH, serum soluble IL-2 receptor, IL-6, TNF-alpha, and IFN-gamma levels are elevated. The brain injury in ANEC presumed to result from a cytokine storm, and increased blood IL-6, TNF-alpha levels in the acute phase of neurological illness correlate strongly with poor outcome. In both ANEC and HLH, hypercytokinemia is essential for the pathogenesis.

CASE REPORTS

- Case 1

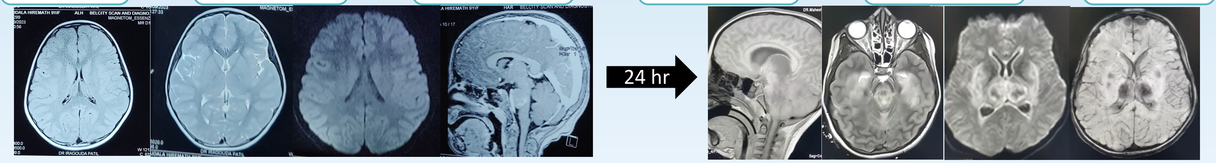
6 yr 3 mon/ F, NCM
Normal birth, development → Fever for 2 days 1 wk back, again for past 2 days → Seizures, altered sensorium since 1 day → Comatose, hypothermia, absent brain-stem reflexes → Hb 10.8, TLC 3800, Plt 1.9, EEG- isoelectric, ferritin- 3434, fibrinogen 172 → Prompt IVMP, but succumbed on day 2



A-E: MRI showing involvement of pons, cerebellum, external capsule, thalami, cortex
F, G: Bone marrow aspirate- histiocyte

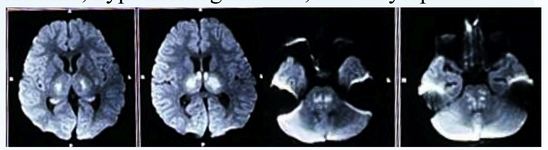
- Case 2

8 yr 2 mon/ F, NCM → Birth, development-normal → Fever- 3 days, Seizures, altered sensorium-2 days → Ventilated and referred after > 24 hrs → Comatose, absent brainstem reflexes → Prompt IVMP, but succumbed on day 2 of admission



- Case 3 6 yr/F - fever, seizures, and altered sensorium. MRI- T2/FLAIR hyperintensities in cerebellum, brainstem, and thalami, with donut sign. She had hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and bicytopenia.

ANE-Severity Scores- 7, 9, and 8, MRI scores- 2, 3, and 3, and serum ferritin (ng/mL) - 3500, 40466, and 1500 respectively for the 3 cases. Exome sequencing negative.



DISCUSSION

CNS-HLH may lack systemic HLH manifestations or typical laboratory abnormalities. Genetic modifying factors may exist that predispose patients to CNS-isolated disease, or specific neuroinflammatory events may lead to CNS involvement without triggering systemic inflammation. 3 patterns are known in HLH: multifocal cerebral/ cerebellar WM lesions (66%), brainstem predominant lesions (15%), and diffuse cerebellar involvement/ cerebellitis (19%). Thalamic involvement is seen in 1/3rd of the HLH cases. Brainstem involvement - predilection for dorsal pons (28%) variably extending to involve midbrain and medulla. ANEC is characterized by multiple and symmetrical lesions with edema and necrosis in the thalamus, the cerebral and cerebellar medulla, and the brainstem tegmentum. Serum ferritin > 1823 ng/mL has about 8 fold increased risk of poor neurological outcome.

CONCLUSION

- Overlap of ANEC and CNS HLH can occur.
- Awareness of this is important for diagnosis and early referral/ institution of immunomodulatory therapy.
- Early use of Tocilizumab <24-48hr or Anakinra can save lives, and have good outcomes in ANEC. Needs to be explored in CNS- HLH.
- Both entities have similar patho-mechanism.
- MRI plays a key role in diagnosis.
- Among novel causes of acute febrile encephalopathy, depending on the area targeted, the brunt may be faced by thalami in ANEC, gray matter in FIRES, gray and white matter in HLH.
- Higher serum ferritin values may be associated with poorer outcomes.

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