

Infection associated haemophagocytic syndrome in severe dengue infection – a case series in a district hospital

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder resulting from uncontrolled hyperinflammatory response. There had been increase in cases of one of the secondary form of HLH, i.e., infection-associated haemophagocytic syndrome (IAHS) in severe dengue in recent years. However, the condition remains under diagnosed due to lack of awareness compounded by the lack of validated diagnostic criteria. Severe hepatitis with prolonged cytopenias, severe hyperferritinemia, hypofibrinogenemia and persistent fever were evident in all four cases reported. All the subjects survived with supportive care and adjuvant steroid therapy. Prospective controlled studies are needed to develop diagnostic criteria and management protocol for IAHS in severe dengue.

KEY WORDS:

Haemophagocytic syndrome, Severe Dengue, Hyperferritinemia, HScore

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon and potential fatal disorder. It is characterised by uncontrolled and dysregulated immune activation which results in cytokine storm. This systemic hyperinflammatory response subsequently leads to multiorgan impairment and failure.¹ It can be classified into primary and secondary. Secondary or acquired haemophagocytic lymphohistiocytosis is further divided into infection associated haemophagocytic syndrome (IAHS), malignancy-associated and autoimmune-associated.² There has been an increase in the incidence of dengue IAHS in the recent years.³ Early detection and intensive supportive care of HLH is vital for survival.

The main challenge in recognising IAHS is because of its wide spectrum of manifestations but lack of specificity in the clinical findings.² Fever, hepatosplenomegaly, cytopenias, hepatitis, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, hyponatremia with haemophagocytosis features on bone marrow are amongst the clinical features that support the diagnosis of HLH.¹ Molecular diagnosis such as pathologic mutations of PRF 1, UNC13D, elevated soluble CD25 and reduced natural killer cell activity are also used in some clinical settings for diagnosis of HLH.² There are no treatment protocol for dengue haemophagocytic syndrome (HS) or any other IAHS. Treatment was mainly supportive. The evidence for

treatment with steroids and intravenous immunoglobulin were mainly anecdotal with variable outcomes in severe dengue.⁵

CASE REPORTS

Patient 1

A 56-year-old Chinese man presented on day six (D6) of illness. He complains of fever and abdominal discomfort. Clinically he appeared very lethargic, dehydrated and bed bound. His highest temperature on admission was 39.2°C. However, he remained well perfused and hemodynamically stable. He had severe hepatitis with alanine transaminase (ALT) and aspartate transaminase (AST) of 1891 µ/L and 4641 µ/L respectively. His serum ferritin was 93026 ng/ml. He also had raised lactate level of 5.0 mmol/L on admission. He was suspected to have HS. He was given intravenous (IV) methylprednisolone 500 mg on D6 and D7 of illness. Bone marrow aspiration and trephine was done on D7 of illness and haemophagocytic activity (Figure 1 and 2) was confirmed. Remarkable clinical and biochemical improvement were observed from D8 onwards. He was discharged well on D16 of his illness. His anaemia resolved without transfusion after two weeks.

Patient 2

A 9-year-old Malay girl was admitted on D6 of illness. She had fever, headache and myalgia. She has haemoglobin of 17.7 g/L, total white cell count of 12,800/µl and thrombocytopenia 32,000/µl. She has clinical signs of hypoperfusion. She also appeared obtunded with a Glasgow Coma Scale (GCS) score of 13/15. She had bilateral up going Babinski reflexes. She was obese with BMI of 25.5, her BMI is more than the BMI of 95th percentile of her age and sex. She had marked haemoconcentration with haematocrit of 52%. A plain computer tomography of the brain on D6 was normal. She was diagnosed to have dengue shock syndrome in compensated shock. She was resuscitated with crystalloids successfully. She had severe hepatitis (ALT 2406 µ/L, AST 7421 µ/L) and acute kidney injury (Urea 19.6 mmol/L, Creatinine 124 µmol/L). She had metabolic acidosis with HCO₃ of 15.7 mmol-1 and lactate of 6.6 mmol⁻¹. Her creatinine kinase was 25,020 Iu/L. She had hyperferritinaemia of 97,316 ng/mL (D7) and hypofibrinogenaemia 0.95 g/L. She was given IV N-acetyl cysteine infusion for acute liver failure. She was given IV methylprednisolone 500 mg twice (total 1g) on D7 of illness due to the persistent encephalopathy and rapidly worsening

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Table I: Clinical characteristics of the patients

Patient No.	Age	NS1 Ag	Hepatitis (ALT or AST >1000)	Highest serum Ferritin (ng/ml)	Serum Fibrinogen (g/l)	Shock	Plasma leakage	Bone marrow evidence of HLH	HScore	HS probability (%)	No. of HLH 2004 criteria fulfilled	Fulfilled HLH 2009
1	56	+	+	93026	2.43	-	-	+	258	99.6	4	-
2	9	+	+	97316	0.95	+	+	NA	176	62	4	-
3	35	+	+	35023	1.79	-	+	NA	200	88	4	+
4	14	+	+	93163	1.86	+	-	NA	216	95	4	+

Note: NS1Ag: non-structural antigen; NA: not applicable; HS: haemophagocytic syndrome; HScore: haemophagocytic score by Fardet et al.⁴

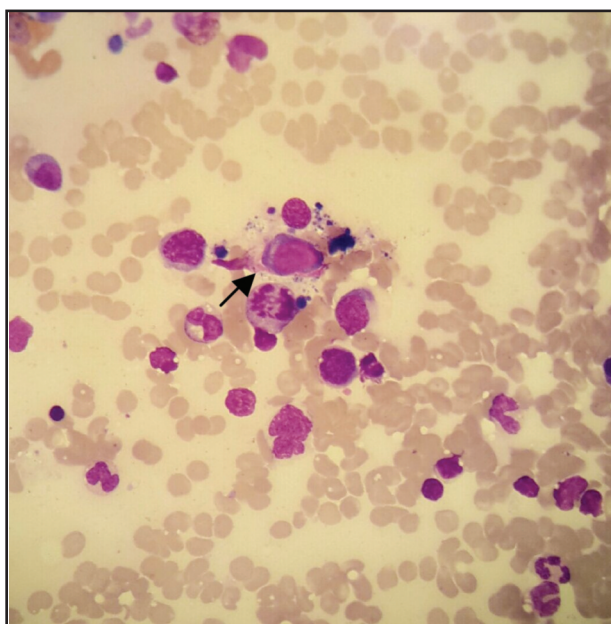


Fig. 1: Engulfment of granulocyte precursor cells by the histiocyte (marked by the black arrow).

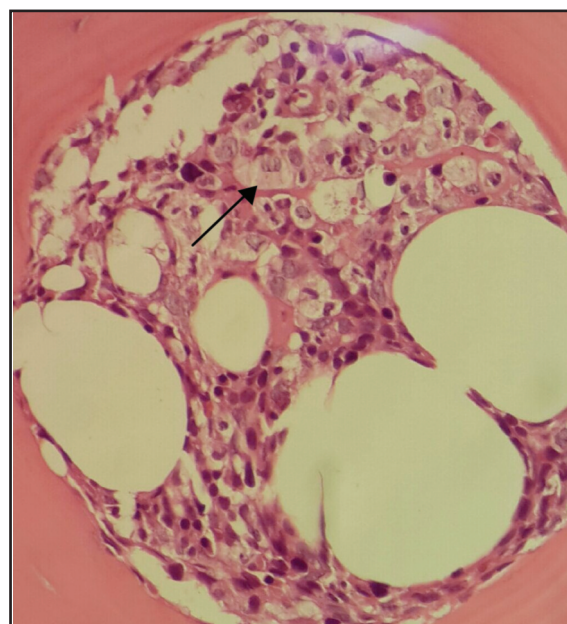


Fig. 2: Trehphine Biopsy showed a large collection of histiocytes feasting on granulocyte precursors (marked by black arrow).

blood parameters in keeping with severe HS. She started to improve from D8 onwards. Her GCS became full and was discharged well on D11 of illness. Her kidney injury resolved spontaneously.

Patient 3

A 35-year-old lady with morbid obesity (BMI 47.3 kg/m²) presented at D3 of fever associated with chills, rigor, vomiting and diarrhoea. She has tachypnoea, tachycardia and tender epigastrium. She was febrile at 38°C. Investigation revealed bicytopenia with haemoglobin 14.9 g/dl, leucopenia 3700/μl, thrombocytopenia 42,000/μl and haematocrit of 43.2%. There was severe hepatitis with highest ALT at 1358 u/l and AST level at 3066 u/l. There was hyperferritinaemia of 35023 ng/ml, hypertriglyceridemia of 3.2 mmol/L and hypofibrinogenemia 1.79 g/L. She required non-invasive ventilation for hypoxaemia. She also had metabolic acidosis as evidenced by bicarbonate level of 13.3mmol⁻¹ and lactate level of 4.9mmol⁻¹. She also developed bilateral pleural effusion. An impression of dengue associated HLH was made and IV methylprednisolone 500mg were given on D4 and D5 of illness. She showed improvement thereafter.

Patient 4

A 14-year-old boy with G6PD deficiency presented with fever for three days associated with vomiting, diarrhoea and spontaneous gum bleed. On D5 of illness he developed hypotension, persistent vomiting and epigastric tenderness. On D6 of illness he had temperature of 39.5°C and was lethargic with poor appetite. His ALT and AST increased to 265 u/L and 864 u/L respectively from a normal baseline on admission. His LDH was also raised at 2719 u/L and serum ferritin doubled to 44,776 g/L. Although his full blood count showed improvement, his temperature and serum ferritin showed otherwise. He had persistent fever with highest spike up to 40.2°C and serum ferritin continues to rise to 81,693 g/L. He was treated as secondary HS and IV methylprednisolone 500 mg was given at D8 of illness. His temperature subsequently subsided and so did his biochemical parameters. He was discharged on D10 of illness. His liver function test gradually returned to normal after two months.

DISCUSSION

In all cases that were reported here, HS was suspected when they developed rapidly raising transaminitis with other supporting features of HS. The HS probability of all patients was calculated using the HScore by Fardet et al.⁴ We understand the HScore was developed and validated for reactive haemophagocytosis and not dengue associated HS.⁴ However, the score seemed to be useful in dengue associated HS when the probabilities are 90% and above as shown in the cases. Patient No. 2 who had a stormier clinical course had the lowest HScore. However, if we presumed that bone marrow aspiration and trephine biopsy was done with evidence of haemophagocytosis, her score will turn out to be 93%. This shows that there is a certain degree of limitation in using the HScore in diagnosing IAHS in dengue fever because not every patient consents for a bone marrow aspiration. Other molecular markers such as the soluble CD 25, natural killer cell activity, and molecular biomarkers are not readily available in most hospitals. Therefore, IAHS in severe dengue may be under diagnosed with the HLH 2004 or proposed HLH 2009 Diagnostic Criteria as these protocols comprise of criteria which involve molecular biomarkers. HScore may be a useful tool which may complement these diagnostic criteria and helps in detecting IAHS. Nevertheless, a high index of suspicion by the clinician based on clinical findings is of utmost importance. HS may still be under recognized if any of the diagnostic criteria or HS scoring system are used solely without taking into consideration the clinical picture as a whole.

CONCLUSION

In severe dengue infection, IAHS need to be taken into consideration if there are evidence of multiorgan involvement, persistent high fever and cytopenias. A deviation of clinical presentation from classical dengue fever should raise a suspicion of the clinician about IAHS.³ The positive outcome in all of the patients in this case series

indicates the potential benefit of steroids in the management of HS in dengue provided that it is recognised and treated early. However, the role of adjuvant therapy is still anecdotal and controversial.⁵ There is no established protocol of its use. The way steroid was used in the cases above was merely based on trial and error. Retrospectively, the justification of its use is still debatable and could only be resolved by randomised control trials.

We feel that HScore is the most user friendly among the HS diagnostic criteria even though none of the diagnostic criteria were validated for IAHS in severe dengue infection. Therefore, until and unless there is a validated HS diagnostic criteria for dengue IAHS, the clinician's judgment is still the most important tool.

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REFERENCES

1. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. *Hematology Am Soc Hematol Educ Program* 2009: 127-31.
2. Mostaza-Fernández JL, Guerra Laso J, Carriedo Ule D, Ruiz de Morales JMG. Hemophagocytic lymphohistiocytosis associated with viral infections: Diagnostic challenges and therapeutic dilemmas. *Rev Clin Esp* 2014; 214(6): 320-7.
3. Tan LH, Lum LC, Omar SF, Kan FK. Hemophagocytosis in dengue: Comprehensive report of six cases. *J Clin Virol* 2012; 55(1): 79-82.
4. 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): 2613-20.
5. Wan Jamaludin WF, Periyasamy P, Wan Mat WR, Abdul Wahid SF. Dengue infection associated hemophagocytic syndrome: Therapeutic interventions and outcome. *J Clin Virol* 2015; 69: 91-5.