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Article in *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology* · June 2015

DOI: 10.1016/j.jcv.2015.06.004

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## Dengue infection associated hemophagocytic syndrome: Therapeutic interventions and outcome

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### ARTICLE INFO

#### Article history:

Received 18 March 2015

Received in revised form 1 June 2015

Accepted 3 June 2015

#### Keywords:

Dengue

Hemophagocytic syndrome

Corticosteroids

Intravenous immunoglobulin

### ABSTRACT

Infection associated hemophagocytic syndrome is increasingly recognized as a potentially fatal complication of dengue fever. It should be suspected with prolonged fever beyond seven days associated with hepatosplenomegaly, hyperferritinemia, worsening cytopenias and development of multiorgan dysfunction. Surge of similar pro-inflammatory cytokines observed in dengue associated hemophagocytic syndrome and multiorgan dysfunction may indicate they are part of related inflammatory spectrum. A proportion of patients recovered with supportive therapy, however most required interventions with corticosteroids, intravenous immunoglobulin or chemotherapy. We report three cases of dengue associated IAHS with good outcome following early recognition and treatment with dexamethasone and intravenous immunoglobulin.

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### 1. Why is this case series important?

Dengue fever (DF) is a self-limiting viral illness but may progress to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The presence of infection associated hemophagocytic syndrome (IAHS) may have significant implication in the management and outcome of patients with dengue infection. Here we report three cases of dengue associated IAHS with a review of similar cases, therapeutic interventions and outcome reported between 1966 and 2014.

### 2. Description of cases

#### 2.1. Patient 1

A 32-year-old male presented on day five (D5) of fever with myalgia, diarrhea and skin rash. The rest of physical examinations were unremarkable. Initial laboratory investigations showed anemia 10.8 g/dL, thrombocytopenia  $116 \times 10^9/L$ , lymphopenia  $0.7 \times 10^9/L$ , acute kidney injury (urea 8.0 mmol/L, creatinine 159 umol/L) and transaminitis with alanine aminotransferase (ALT) 378 U/L and aspartate transaminase (AST) 1132 U/L. Dengue serology IgM was positive with negative IgG, indicative of primary dengue infection. On D7 of fever, he developed splenomegaly, hypotension, metabolic acidosis, worsening cytopenias, hematuria and nephrotic syndrome (proteinuria 2945 mg/24 h, hypoalbuminemia 28 g/L). Empirical antibiotics were administered although later microbiology investigations for secondary infections were negative. Dengue associated IAHS was suspected based on the presence of hyperferritinemia  $>40,000 \text{ mg/L}$ , hypertriglyceridemia 10.37 mmol/L, hypofibrinogenemia 1.8 g/L and markedly elevated lactate dehydrogenase (LDH) 5101 U/L. Bone marrow (BM) biopsy on D9 of fever showed hemophagocytosis. Intravenous (IV) dexamethasone 10 mg/m<sup>2</sup> daily was given on D9 and intravenous immunoglobulin (IVIG) of 0.5 g/kg was administered 48 h later due to lack of initial response. Dexamethasone was tapered down after

**Abbreviations:** DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; IAHS, infection associated hemophagocytic syndrome; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; IV, intravenous; IVIG, intravenous immunoglobulin; MOD, multiorgan dysfunction; NS1, non-structural protein 1; IA, invasive aspergillosis; IL-, interleukins; TNF, tumor necrosis factor; IFN, interferon; SIRS, systemic inflammatory response syndrome.

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Author [Reference]	Number of patients	Age (years)	Fever duration (days)	Dengue type	Plasma leakage	Transaminitis Lymphopenia (ALT or AST level $\times 10^9$ /L in U/L)	MOD	Coagulopathy	Ferritin mg/L	Outcome
Jain [2]	1	14	14	DHF, secondary	No	N/A	No	No	N/A	Alive
Tan [4]	2	16	>7	DHF, primary	Yes	Yes (2296)	N/A	No	28,060	Alive
Ramanathan [10]	1	20	4	DHF, primary	Yes	Yes (916)	N/A	No	56,640	Alive
Lu [11]	1	19	8	DHF, secondary	No	Yes (112)	0.8	No	N/A	Alive
	1	33	10	DHF, primary	Yes	Yes (179)	N/A	Yes	N/A	Alive

two weeks with resolution of fever and splenomegaly, followed by normalization of all blood results.

### 3. Patient 2

A 19-year-old male presented on D4 of fever with headache, myalgia, vomiting and epigastric pain. Clinically he had tender hepatomegaly, ascites and pleural effusion. Dengue serology was positive for both IgG and IgM, indicative of secondary dengue infection. Initial laboratory investigations showed critical phase of DHF and subsequently developed anemia 8.0 g/dL, thrombocytopenia  $25 \times 10^9$ /L, lymphopenia  $0.8 \times 10^9$ /L, transaminitis (ALT 5236 U/L, AST >7000 U/L) and acute kidney injury (urea 25.1 mmol/L, creatinine 452 umol/L). He deteriorated with lactic acidosis and multiorgan dysfunction (MOD). All microbiological investigations for secondary infection were negative. Dengue associated IAHS was suspected based on the presence of hyperferritinemia >40,000 mg/L, hypertriglyceridemia 1.54 mmol/L and a high LDH 1399 U/L. Dexamethasone 12 mg in three divided doses was started on D5 for two days. The fever resolved immediately and he was discharged well after three weeks with normalization of all blood results.

### 4. Patient 3

A 17-year-old male presented on D2 of fever with DSS as evidenced by abdominal pain, hepatomegaly, hypotension and positive for non-structural protein 1(NS1) antigen. Initial laboratory investigations showed pancytopenia (hemoglobin 11.9 g/dL, lymphopenia  $0.6 \times 10^9$ /L, thrombocytopenia  $40 \times 10^9$ /L), acute kidney injury (creatinine 134 umol/L, urea 6.8 mmol/L) and transaminitis (ALT 234 U/L, AST 173 U/L). He received empirical antibiotics although later all microbiological investigations were negative. Dengue associated IAHS was suspected on D6 of fever based on the presence of hyperferritinemia 17,432 mg/L, hypertriglyceridemia 2.06 mmol/L and raised LDH 1054 U/L. Three doses of dexamethasone 4 mg were given on D6 of fever, followed by resolution of symptoms and normalization of all blood results.

### 5. Other similar and contrasting cases in the literature

Review of literature in the English language yielded less than thirty reports on dengue associated IAHS between 1966 and 2014, in both pediatric and adult patients. Severe dengue is a recognized cause for IAHS in Southeast Asia but overall worldwide incidence remains low between 2% and 35.7% [1–9].

Four authors reported resolution of dengue associated IAHS with supportive treatments in four adult patients (range 16–33 years) and one pediatric patient (14 years) [2,4,10,11]. Mean duration of fever was 8.6 days (range 4–14 days). All patients had DHF, three with primary and two with secondary dengue infections. Severe plasma leakage occurred in three patients. Diagnostic BM biopsy was performed in four patients. Three patients had leucopenia; one developed lymphopenia  $0.8 \times 10^9$ /L. All but one developed transaminitis. Serum ferritin level was available in two patients; 28,060 mg/L and 56,640 mg/L. The diagnosis was made based on persistent fever, pancytopenia, hyperferritinemia, hepatosplenomegaly and BM biopsy. All patients received supportive treatments only and recovered well (Table 1).

Fourteen reports described favorable outcome after specific therapy with corticosteroids and/or IVIG with variable treatment regimes [1,3,4,7,9,12–19]. There were a total of 61 patients, with 18 adults (range 16–46 years) and 43 pediatrics (range 50 days–15 years). Mean duration of fever was 11 days (range 3–21 days). Dengue associated IAHS occurred in nine primary and four sec-

**Table 2**

Outcome of dengue associated IAHS with specific treatments.

Author [Reference]	Number of patients	Age (years)	Fever duration(days)	Dengue type	Plasma leakage	Transaminitis (ALT or AST in U/L)	Lymphopenia (level $\times 10^9/L$ )	MOD	Coagulopathy	Ferritin mg/L	Treatment	Outcome
Ramachandran[15]		<14	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Dexa, MP, IVIG, CSA, VP16	N/A
Ray [3]	1	24	7	DHF, primary	Yes	Yes	N/A	No	Yes	2161	Dexa	Alive
Tan[4]	4	16	8	DHF, primary	Yes	Yes (2167)	N/A	Yes	N/A	36484	MP & IVIG	Alive
		43	6	DHF, secondary	Yes	(2296) Yes	N/A	Yes	N/A	154300	MP	Died
		34	4	DHF, primary	Yes	(666) Yes	N/A	No	N/A	37678	MP	Alive
		36	7	DHF, secondary	No	(1121)	N/A	No	N/A	20569	MP	Alive
Pal [7]	8	<15	>7	DHF	Yes	Yes in 7	N/A	Yes	Yes	1832–64600	Dexa in all 8, & IVIG in 1	All alive
Raju [8]	23	<3	13.96	DF & DHF	Yes	Yes (1780)	N/A	Yes	Yes	600	IVIG in 19	19 alive
Sorakunpipitkul [9]		16–65	N/A	DHF	Yes	Yes in 4	N/A	Yes	Yes in 4	N/A	Dexa, MP, IVIG	5 alive, 2 died
Ribeiro [12]	3	44	4	DF, primary	No	Yes	N/A	No	No	9600	CS	Alive
		33	3	DF, primary	No	Yes	N/A	No	No	23451	CS & IVIG	Alive
		25	N/A	DF, primary	No	Yes	N/A	No	No	7093	MP	Alive
De Koninck [13]	1	21	3	DF, secondary	No	Yes (563)	Yes (0.3)	No	Yes	13700	IVIG	Alive
Giri [14]	2	<15	>7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Dexa	Both alive
Veerakul [15]	3	<13	>21	DHF in 1	N/A	Yes in 1	N/A	Yes in 1	N/A	N/A	IVIG in 1	1 died
Kapdi [16]	1	4	15	DHF, primary	Yes	Yes (290)	Yes (0.75)	No	No	7309	CS & CSA	Alive
Mitra [17]	1	2	10	DHF, primary	Yes	Yes (1675)	N/A	No	Yes	11220	Dexa	Alive
Roy [18]	1	22	7	DHF, primary	Yes	Yes (435)	Yes (1.4)	Yes	Yes	6700	Dexa	Alive
Srichaikul [19]	1	46	4	DHF, secondary	Yes	Yes (1344)	Yes (1.65)	Yes	Yes	7095	MP& IVIG	Alive
Wan Jamaludin [current author]	3	32	9	DHF, primary	Yes	Yes (ALT 378, AST 1132)	Yes (0.7)	Yes	Yes	>40000	Dexa, IVIG	Alive
		19	5	DHF, secondary	Yes	Yes (ALT 5236, AST > 7000)	Yes (0.8)	Yes	No	>40000	Dexa	Alive
		17	6	DHF, primary	Yes	Yes (ALT 234, AST 173)	Yes (0.6)	Yes	Yes	17432	Dexa	Alive

Abbreviations: Alanine aminotransferase (ALT); aspartate transaminase (AST); multiorgan dysfunction (MOD), dengue hemorrhagic fever (DHF), dengue fever (DF), dexamethasone (Dexa), methylprednisolone (MP), corticosteroid (CS), intravenous immunoglobulin (IVIG), cyclosporin A (CSA), etoposide (VP16), not available (N/A).

ondary dengue infections, and 48 patients had DHF/DSS whereas 4 patients had classical DF (where available). Plasma leakage was reported in 46 patients. Pancytopenia was present in all patients. MOD occurred in 43 cases. Lymphopenia range was between 0.3 and  $1.65 \times 10^9/L$  (where available). Coagulopathy was reported in 39 patients. Serum ferritin level ranged between 600 and 154,300 mg/L. BM biopsy was performed in 42 patients. Four reportedly died despite specific therapy (Table 2).

Fatal dengue associated IAHS were reported in four previously healthy children with postmortem findings of invasive aspergillosis (IA) [20]. The damaged respiratory mucosa due to DSS and impaired immunity due to IAHS may have contributed to the pathogenesis of IA. Another two fatal cases; one was primary and another secondary dengue infection were also reported [21,22]. Severe marrow hemophagocytosis was found at postmortem in seven DHF cases and in biopsy of two DHF survivors [23]. This phenomenon was not observed in other milder DHF in whom BM was performed at the same time [19], raising the possible temporal relation between dengue associated IAHS and severity of DHF.

## 6. Discussion

In DF the febrile phase lasts up to seven days. With prolonged fever, secondary bacterial infection should be excluded and dengue associated IAHS should be suspected. Severe or fatal complications may ensue if dengue associated IAHS is unrecognized. Both Patient 2 and Patient 3 received dexamethasone before D7 of fever due to early recognition of dengue associated IAHS based on the presence of persistent pancytopenia, MOD, hyperferritinemia, hypertriglyceridemia and raised LDH. Defervescence occurs between D3 and D7 and in DHF this period is associated with critical phase and plasma leakage. Secondary dengue infection (two sequential infections by different serotypes) is also a risk for severe dengue. However, we and others [3,4,12,16–18] observed that primary dengue infections were as much at risk of severe DHF and dengue associated IAHS. Primary dengue infection with serotype 1 or 3 and secondary infection with serotype 2 can lead to severe DHF [24]. Hematopoietic suppression occurs on D4–D5 due to inhibitory effect of pro-inflammatory cytokines such as interleukins (IL-6 and IL-8), tumor necrosis factor (TNF) and interferon (IFN) [25]. Generation of autoantibodies and molecular mimicry between platelets/endothelial cells and dengue antigens are also responsible for cytopenias [25]. Activation of immunoregulatory T-lymphocytes are more evident in DHF than in classical DF during the febrile phase with significant reduction of lymphocyte subsets possibly due to immune elimination of dengue virus and cell lysis [26].

HS is a hyperinflammatory condition due to hyperactivation of lymphocytes and macrophages with resultant cytokine storm, leading to organ dysfunction and death. It is classified into familial or secondary to infection, malignancy, or rheumatological conditions. Familial HS is caused by genes mutations in the cytolytic secretory pathway [27]. Pathogenesis of secondary HS is less defined, although they may have heterozygosity for polymorphisms in the familial HS genes. Clinically, it is difficult to distinguish between familial and secondary forms as both may present with similar clinical features. Diagnostic criteria in the HLH-2004 guidelines require a minimum score 5 of 8 (Table 3) [39].

Dengue induced endothelial dysfunction leading to renal filtration abnormalities has been proposed [28,29]. This may account for nephrotic syndrome in our patient. Histologically glomerulopathies and thrombotic microangiopathy with abnormal podocytes were described, and elevations of pro-inflammatory cytokines were thought to be responsible [30].

**Table 3**

Diagnostic guidelines for HLH-2004 [39].

Diagnostic Guidelines For HLH-2004	
The diagnosis	HLH 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 (5 out of the 8 criteria below)	A) Initial diagnostic criteria:
Clinical criteria:	Fever
Laboratory criteria:	Splenomegaly
Histopathologic criteria	Cytopenias (affecting $\geq 2$ of 3 lineages in the peripheral blood)
B) New diagnostic criteria	Hypertriglyceridemia and/or hypofibrinogenemia
Low or absent NK-cell activity	Hemophagocytosis in bone marrow or spleen or lymph nodes
Ferritin >500 mg/L	No evidence of malignancy
Soluble CD25 (i.e., soluble IL-2 receptor) $\geq 2400 \text{ U/mL}$	

The presence of both dengue associated IAHS and MOD in majority of the patients may indicate they are part of an inflammatory spectrum, which also include systemic inflammatory response syndrome (SIRS) [31]. IL-6 and TNF are associated in the pathogenesis of MOD [32,33] and high serum concentrations of IL-6, IFN alpha, and IL-2 receptor are associated with poor prognosis [34]. Nonetheless, treatment for each syndrome is different as HS is treated with chemo-immunotherapy whereas supportive therapy is keystone in SIRS and MOD [31].

While nonsense and frameshifts mutations lead to a complete loss of gene function in familial HS, missense mutations cause only a partial loss. Polymorphism may also influence disease presentation [35]. These may explain the variable therapeutic responses observed in dengue associated IAHS with supportive therapy, corticosteroids and IVIG. Role of plasma exchange in steroid refractory IAHS have been described [36–38].

## 7. Conclusion

Dengue associated IAHS must be suspected in the presence of persistent fever beyond D7, hyperferritinemia more than 20,000 U/L, worsening cytopenias, shock and MOD beyond plasma leakage phase. BM biopsy should be performed to demonstrate hemophagocytosis. Exclusion of SIRS and secondary infection is important before initiation of corticosteroids. Early recognition has a significant impact on the management and outcome. Dengue associated IAHS may indicate a severe form of dengue infection, and dengue virus needs to be recognized as an important causative agent for IAHS.

## Funding

None to disclose.

## Competing interests

None to declare.

## Ethical approval

Not required.

## Acknowledgements

The authors thanks Mrs Nor Azimah Ismail, Cell Therapy Center and Universiti Kebangsaan Malaysia Medical Center.

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