Journal of Clinical Virology 69 (2015) 91–95

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

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.

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 116×10^9/L, lymphopenia 0.7×10^9/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 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^2 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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http://dx.doi.org/10.1016/j.jcv.2015.06.004
1386-6532/

Table 1
Outcome of dengue associated IAHS with supportive 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	Outcome
Jain [2]	1	14	14	DHF, secondary	No	No	N/A	No	No	N/A	Alive
Tan [4]	2	16	>7	DHF, primary	Yes	Yes (2296)	N/A	No	No	28060	Alive
		20	4	DHF, primary	Yes	Yes (916)	N/A	No	No	56640	Alive
Ramanathan[10]	1	19	8	DHF, secondary	No	Yes (112)	0.8	No	No	N/A	Alive
Lu [11]	1	33	10	DHF, primary	Yes	Yes (179)	N/A	No	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 25×10^9/L, lymphopenia 0.8×10^9/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

A17-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 0.6×10^9/L, thrombocytopenia 40×10^9/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 0.8×10^9/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-