Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 08, Issue, 01, pp.4141-4143, January, 2017

RESEARCH ARTICLE

MACROPHAGE ACTIVATION SYNDROME IN SECONDARY DENGUE: A RARE PRESENTATION

***Dr Tapan Biswas**

Infectious Disease and Beliaghata General Hospital, Kolkata -10, West Bengal, India

ARTICLE INFO

Article History:
Received 19th October, 2016
Received in revised form
27th November, 2016
Accepted 18th December, 2016
Published online 31st January, 2017

Key words:

Macrophage Activation Syndrome,
Secondary Dengue,
Multi-organ dysfunction in dengue,
Hyperferritinemia in severe dengue.

ABSTRACT

We describe a 60 year old female developing dengue-associated macrophage *activation* syndrome. The condition was diagnosed according to the established criteria of the International Histiocyte Society and Application of H-score. Patient was full recovery with corticosteroid therapy. Macrophage activation syndrome in adult mimic severe sepsis, systemic inflammatory response syndrome, or multi organ dysfunction syndrome and lead to diagnostic difficulties. This report adds to the limited adult cases of dengue related macrophage activation syndrome in literature. This documentation is presented because of a rare manifestation of a common disease. The importance of diagnosis and appropriate treatment of this rare case will enlight in dengue related literature. The outbreak of dengue in West Bengal in 2016 will more complicated in future as secondary dengue.

INTRODUCTION

Dengue is a mosquito borne human disease. Worldwide infected about 3.2 million/year. (WHO, 2015) One recent estimate indicates 390 million dengue infections per year (WHO, 2016) Half of the world population is now at risk. (WHO, 2016) An estimated 5 lakh people with severe dengue required hospitalization each year and 2.5% die. (WHO, 2016) India is a tropical country and endemic zone of dengue fever. A number of people were affected by this disease in this rainy season (2016) in the city of Kolkata, India; during dengue outbreak in West Bengal. (*Anandobazar Patrika,* 2016) Most of them were non-complicated but some them were fatal. It is a single disease entity with different clinical presentations, and is classified into dengue and severe dengue, based on the extent of plasma leakage, bleeding and organ involvement. (World Health Organization, 2009) Hemophagocytosis is a rare complication of dengue fever (LuPl *et al.,* 2005). Macrophage activation syndrome (MAS), or haemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disease (Ashok Duggal, 2010). It is of two types primary HLH, and secondary HLH (acquired HLH) which occurs after strong immunologic activation of systemic infection (virus, bacteria, and protozoa), autoimmune disorders, or an underlying malignancy. In recent decades, an uncommon phenomenon of macrophage activation syndrome (MAS) or hemophagocytic syndrome (HS) is increasingly reported in patients with severe dengue (Hasliana Azrah *et al.,* 2016).

****Corresponding author: Dr Tapan Biswas***
Infectious Disease and Beliaghata General Hospital, Kolkata -10, West Bengal, India.

The underlying immune defect and/or triggering events result in an abnormal immune response with activation of certain types of white blood cells (lymphocytes and macrophages) and the release of inflammatory proteins are the cause of macrophage activation syndrome. The true cause of HLH/FHL is not known. MAS is a severe systemic inflammatory condition due to excessive activation and proliferation of T cells and well-differentiated macrophages. The hyperactivated but dysregulated immune responses lead to overwhelming inflammatory responses resulting in non-remitting high fever, hepatomegaly and splenomegaly, lymphadenopathy, haemorrhage and central nervous system dysfunction (Ravelli *et al.,* 2015).

Secondary hemophagocytic syndromes/hemophagocytic lymphohistioc ytosis can arise in the setting of malignancies, autoimmune disorders, or viral and bacterial infections like Epstein–Barr virus, cytomegalovirus, parvovirus, herpes simplex, HIV or tuberculosis. Infection associated hemophagocytic syndrome carries a high mortality. The clinical manifestations can overlap with those seen in severe sepsis, systemic inflammatory response syndrome (SIRS), or multiorgan dysfunction syndrome (MODS). In severe dengue, a number of cytokines like IL1, IL2, IL6, TNFalfa, soluble soluble CD8 are released. Elevation of TNF alfa, IL6, IL8, IL10, chokines, INFgama have been reported in the patients with serve dengue. (11) IL-1β, IFN-γ, IL-4, IL-6, IL-13, IL-7 and GM-CSF were significantly increased in patients with severe clinical manifestations of severe dengue (Multiplex cytokine profile from dengue patients, 2008). This

hypercytokinemia leads to systemic manifestations and progressive organ dysfunction. The International Histiocyte Society has laid down a newer set of diagnostic criteria to aid in quicker diagnosis and institution of appropriate therapy. Histiocyte Society—HLH can be established in the presence of (i) molecular diagnosis consistent with HLH or (ii) the presence of five out of eight criteria, namely, fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in tissue, hyperferritinemia, increase in CD25/IL-2 receptor or reduced NK cell function.

Current diagnostic criteria for HLH is given here

- Fever
- Splenomegaly
- Cytopenia(affecting atleast 2 out of 3 lineages in peripheral blood.(Hemoglobin <9 g/100 ml (in infants <4 weeks: hemoglobin <10 g/100 ml; Platelets <100 103/ml, Neutrophils <1 103/ml)
- Hypertriglyceridemia (fasting, ≥265 mg/100 ml) and/or hypofibrinogenemia (≤150 mg/100 ml)
- Hemophagocytosis in Bone marrow, spleen or lymph nodes
- Low or absent NK cell activity
- Ferritin 500 ng/ml
- Soluble CD25 (that is, soluble IL-2 receptor) >2400 U/ml (or per local reference laboratory)

CASE

A 60yr old female, from city of Kolkata, West Bengal, India has been admitted in a private medical Institute with c/o high fever associated alter sensorim for 4 days without an episode of convulsion. On examination –patient's GCS9/15, Temparature - (40°C/104°F), pulse 120/minute, BP-90/60, purpuric spot on body, without neck rigidity and normal planter response and others parameter were normal. Possible differential diagnosis were meningoencephalitis, cerebral malaria, septic encephalopathy and viral fever with metabolic abnormality. Her CBC shows platelate count 45,000/cmm and fall upto 20,000/cmm; WBC-7,200/cmm, HB-7.5gm/dl. Her creatinine was 1.0mg/dl and bilirubin was 3.53 mg/dl,AST-228IU/L,ALT-282IU/L ,Albumin-2.13gm/dl. Others reports eg. MP, Dual antigen, metabolic panel, CRP, PT& APTT all were normal. Due to thrombocytopenia and epidemic of dengue we sent NS1Ag, Dengue IgM antibody on 5th day of fever and all were positive(by ELLISA). Blood and urine culture were negative. After 5days gap her platelate rose 80,000/cmm but raised AST-333 iu/l and ALT-178iu/l. To know the severity of dengue we sent serum Ferritin and it was excessively high-25,185 ng/ml. Then we though it may a case of Macrophage Activating Syndrome . And it was found that serum fasting Triglyceride was 459mg/dl; Fibrinogen 144mg/dl. USG abdomen shown hepato-spleenomegaly without any ascites. CT brain was normal. Leptospira IgM was sent due to high CPK-4198 but it was negative. Soluble CD25 (that is, soluble IL-2) could not be measured due to financial constrain. We have treated her with iv paracetamol, platelate transfusion, IVF and PPI. Latter we added iv dexamethasone 10mg once daily for five days and full recovered. Bone marrow was not done due to severe thrombocytopenia. She had h/o dengue fever on 3 month back and lowest platelate count was 1.06 lakh and diagnosed by positive of NS1Ag and IgM. (by Ellisa method)

DISCUSSION

The patient condition met the diagnostic criteria of hemophagocytic syndrome which include fever, hepato-splenomegaly, jaundice, bicytopenia, hypertriglycerdenia, hypofibrinogenemia, hyperferitinemia. Hemophagocytosis is a rare complication of dengue fever (Lu *et al.,* 2005). Virus associated hemophagocytosis syndrome is a rare disease characterized by fever, splenomegaly, cytopenia and histiocytic proliferation with hemophagocytosis in reticuloendothelial system.

There are two types of hemophagocytic syndrome. The primary or familial type is an autosomal recessive disorder that affects children and is usually fatal, where as secondary or reactive type is associated with viral,bacterial, fungal or parasitic infection. It may be associated with connective tissue disorders and malignancy. The pathogenesis is not clear. Many believe that viral infection provokes an abnormal immune response in predisposed individuals leading to hyper activation of the helper cells, macrophage proliferation and secretion of large amount of cytokines. It is classified as one of the cytokine storm syndromes or cytokine tsunami. The resultant hypercytokinemia may be responsible for clinical and bio-chemical manifestation of hemophagocytic syndrome. Proposed diagnostic clinical criteria for hemophagocytic syndrome are fever, splenomegaly, hepatomegaly, lymphadenopathy, rash and neurological syndrome; And laboratory abnormality include anemia, thrombocytopenia, neutropenia, hypertriglyceridemia, hypofibrinogenenia and increased ferritin level.

In our case patient had dengue fever with hepato-spleenomegaly, bicytopenia, raised triglycerides, decreased fibrinogen level and increased ferritin level. The aim of treatment is suppression of increased inflammatory response and control of cell proliferation using immunosuppressive or immunomodulatory agents and cytotoxic drugs. Chemotherapy like Dexamethasone, Cyclosporine and Etoposide are also used. Since our patient responded to Dexamethasone therapy alone other chemotherapy drugs were not added. Role of immunoglobulin in treatment of hemophagocytic syndrome is not clear. For patients with genetic hemophagocytic syndrome and severe or refractory hemophgocytic syndrome bone marrow transplantation should be considered. The use of growth factors such as granulocyte colony stimulating factor or GM-CSF can exacerbate hemophagocytic syndrome and hence not used. Hemophagocytic syndrome associated with infectious illness may resolve with treatment of underlying infection. Our patient is an unusual case of dengue-related hemophagocytic syndrome and contributes an additional case to the existing literature on this topic. The occurrence of typical laboratory findings include bicytopenia or pancytopenia, hepatic impairment with coagulopathy, hypofibrinemia, elevation of serum LDH and triglyceride levels, and ferritinemia (Hemophagocytic Syndrome in Classic Dengue Feve). Reactive eg infection-associated hemophagocytosis is rare and that too in the setting of classic dengue fever. Clinicians should be aware of the fact that the occurrence of hemophagocytosis and dyserythropoiesis could

be due to dengue virus infection in areas where the disease prevalence is more; And more commonly seen in secondary dengue. In this case, there is involvement of central nervus system as we found her GCS was 9/15. This may add additional finding in MAS. In this case we got purpuric spot on arm and other part of body and it is due to low platelate count (45000/cmm). Her CPK was 4198iu/l and it is very high; additional finding in severe dengue. In this case CSF was not done due to severe thrombocytopenia. Low blood pressure was not due to capillary leak syndrome as in USG shown only hepato-spleenomegaly without any evidence of ascites. Hepatic involvement is well documented in severe dengue.(14) We have calculated her H-score and result is 262 . So, probability of MAS is 99.71%. (15)-http://saintantoine.aphp.fr/score/

Conclusion

Hemophagocytic syndrome is a very rare complication of Dengue Fever. Since dengue fever is very much prevalent in our country and is increasing day by day more awareness should be created for prompt recognition and early institution of appropriate therapy which is the most important factor for recovery. Dengue may complicated with multiorgan dysfunction syndrome. Most of the complication are observed in secondary dengue.

Acknowledgments

We acknowledge the vital role of paramedical staff and lab technician in that medical institute in providing the proper medical care for these patient. We also acknowledge others physician and medical officer who encouraged us to persue the cases.

Consent: Informed consent is taken from the patient.
Conflict of Interest: No conflict of interest is decleared.

REFERENCE

World Health Organization (2009) Dengue: guidelines for diagnosis, treatment, prevention and control. WHO Press, Geneva

LuPl, Hsiao, H.H., Tsaj, J.J., Chen, T.C., Fency, M.C., Chen, T.P., Lin, S.F. 2005. Dengue virus associated hemophagocytic syndrome and dys erythropoeisis. Kaohsiung *J Med Sci.,* 21(1):34-9.

Macrophage Activation Syndrome-Ashok Duggal, Gurminder Kaur, *JIACM*, 2010;11(1):63-5

Hemophagocytic Syndrome-A Rare Complication of Dengue Fever -Rabia Rathore ey all -124-ANNALS/ VOL 18/NO.1JAN.-MAR/ 20123.

Macrophage Activation Syndrome-Associated Markers in Severe Dengue byHasliana Azrah Ab-Rahman et all in *Journal List Int J Med Sciv.,* 13(3); 2016,PMC4773282-Published onlin 2016Feb17.doi: 10.7150/ijms.1368

Ravelli, A., Magni-Manzoni, S., Pistorio, A. et al. 2005. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Pediatr.,* 146:598–604. [PubMed]

Inflammation and Innate immune Response in Dengue infection; *The American Journal of pathology*, June 2013, volume-182(6).

Multiplex cytokine profile from dengue patients: MIP-1beta and IFN-gamma as predictive factors for severity-Fernando A Bozza, et all -BMC Infectious Diseases20088: 86; DOI: 10.1186/1471-2334-8-86 ;© Bozza et al; licensee BioMed Central Ltd. 2008; Published: 25 June 2008

Hemophagocytic Syndrome in Classic Dengue Feve J Glob Infect Dis. 2011 Oct-Dec; 3(4): 399–401. doi: 10.4103/0974-777X.91068.PMCID: PMC32500017.

Profile of liver function test in patients with dengue infection in South. www.mjdrdypu.org/article.asp?issn=0975-2870; year=2013; volume=6, by K Gandhi - 2013.

http://saintantoine.aphp.fr/score/

WHO, May 2015; Dengue and Severe Dengue.

WHO, April 2016, Fact update sheet; Dengue and severe Dengue *Anandobazar Patrika; A daily News. Date 15/8/2016*

WHO |Dengue and severe dengue-Fact sheet Updated July 2016; www.who.int/mediacentre/factsheets/fs117/en/

****