Section: Microbiology

Case Series

SIGNIFICANCE OF CYTOKINE PROFILING IN PATIENTS WITH "WARNING SIGNS OF DENGUE" – CASE SERIES

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ABSTRACT

We present four interesting and important cases of dengue referred to our tertiary care hospital with a diagnosis of undifferentiated febrile illness. All four presented presented with high grade fever associated with gastrointestinal manifestations predominantly. Characteristic features of dengue were absent in both the patients. Dengue disease was confirmed based on serology. Patients had developed warning signs of dengue, however the patient with primary dengue progressed to severe dengue and other patient with secondary dengue recovered completely. All the patients were positive for DENV-1by CDC multiplex rRT-PCR .Cytokines IL-6, 8, 10, INF-γ, TNF α; indicators of hemorrhagic dengue disease was analysed. Interestingly patient with secondary dengue recovered from the illness with increase in platelets and a significant reduction of pro-inflammatory cytokines in the convalescent phase. Whereas patients with primary dengue progressed to severe dengue with evident hepatic failure he subsequently developed a decompensated shock which correlated with elevated IL-6, 8 and IL-10 levels and clinically with pleural effusion and ascites.

INTRODUCTION

Four adult patients were referred to our tertiary care hospital with a diagnosis of undifferentiated febrile illness. All presented with high grade fever and gastrointestinal manifestations. Owing to the ongoing dengue epidemic dengue serology was done and all were confirmed to be having dengue fever. All the patients were admitted as they had features of dengue with warning signs. Dengue viremia (DENV-1) was confirmed by CDC Real time RT-PCR. Pro-inflammatory and anti-inflammatory cytokines IL-6, 8, 10, INF-γ, TNF α were analysed for all the patients. Interestingly patients with secondary dengue recovered from the illness with a significant reduction of pro-inflammatory cytokines in the convalescent phase. Whereas patient with primary dengue progressed to severe dengue with evident hepatic failure he subsequently developed a decompensated shock due to multi-organ failure. Clinical conditions correlated with elevated cytokines in all the cases.[1]

Dengue viruses are the most important vector-borne viral disease of public health importance causing acute undifferentiated febrile illnesses. Though most of the patients develop only a self - limiting febrile illnesses, severe dengue is not uncommon especially during epidemics in the tropical countries. Complications like hemorrhagic fever /shock syndrome, hepatitis, encephalitis, myocarditis and Haemopagocytic lymphohistiocytosis (HLH syndrome) have been reported from the dengue endemic areas. Due to the complex immunopathogenesis and antibody dependant enhancement in secondary dengue is generally associated with DHF/DSS. During epidemics, DHF cases among patients with primary dengue infections have been documented (Barnes & Rosen 1974, Scott et al. 1976, Rosen 1977). Due to co-circulation of other arboviruses like Chikungunya and other infections like malaria, leptospirosis, enteric fever in the dengue endemic countries clinical diagnosis of dengue is difficult. It is important that cases presenting with atypical features should be brought into notice for the clinicians to aid in early identification of dengue.[2]

The varied disease spectrum and the fact that a single diagnostic test may not be sufficient to conclude dengue diagnosis is challenging for the treating physician. Currently dengue diagnosis is based on serological methods. Molecular methods for DENV are used only for epidemiology purpose. Factors like viral serotype, secondary infections and cytokine profile are associated with DHF/DSS four serotypes. Cytokine storm in dengue with a shift from TH1 to TH2 has been postulated as the reason for sudden

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clinical worsening. Several cytokines have been associated with these detrimental effects in dengue. However, there is need for clinical studies to better understand the role of cytokine in dengue. (Iyngkaran et al. 1995). (Braga et al. 2001, Nguyen et al. 2004, Perez et al. 2004, Bozza et al. 2008, Restrepo et al. 2008a, b).

Delay in diagnosis / under-reporting and lack of hospitalization of dengue cases during the outbreaks is a major issue for the public health systems especially in the developing countries where bed occupancy rates are already high. In this case series we attempted to correlate few atypical dengue cases with serological, virological and cytokine profiles.[3]

CASE

Case 1

A 32-year-old male was referred from a primary care centre situated in a rural area endemic to dengue disease with a history of high grade intermittent fever for duration of four days with associated complaints of vomiting. Typical symptoms of dengue rash, arthralgia, headache, retro-orbital pain were absent. Patient did not have any bleeding manifestations. Patient was apparently normal and there were no other known co-morbidities.

Case 2

A 42-year-old male patient came with complaints of high grade intermittent fever with associated myalgia. Patient had history of vomiting and few episodes of loose stools. Patient did not have any bleeding manifestations. Past medical history was insignificant.

Case 3

A 34-year-old female patient with high grade intermittent fever with associated myalgia and retroorbital pain. Patient had history of vomiting and abdominal pain. Did not have any bleeding manifestations.

Case 4

A 28-year-old male with high grade intermittent fever, severe myalgia, abdominal pain and nausea with loose stools. Initially thought to be AGE later confirmed Dengue by PCR and serology.

Table 1

Laboratory values	Patient 1	Patient 2	Patient 3	Patient 4
WBC	4,700/cu mm	2,200/cu mm	3,100/cu mm	4,100/cu mm
Platelets	33,000/Cu Mm Day Of Illness	22,000/Cu Mm Day Of Illness	45,000 /cu mm	65,000 /cu mm
Liver Enzymes				
ALP	262 U/L	91U/L	234 U/L	88 U/L
SGOT	3803 U/L	72U/L	125 U/L	54 U/L
SGPT	1180 U/L	152 U/L	112 U/L	78 U/L
Imaging Studies				
X-RAY	Right Pleural Effusion	No Significant findings	No Significant findings	No Significant findings
USG	Minimal Ascites	No Significant findings	Minimal Ascites	No Significant findings

Table 2

Virology Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Dengue NS1	Positive	Positive	Positive	Positive
Dengue IgM	Negative	Positive	Positive	Positive
Dengue IgG	Negative	Positive	Positive	Negative
Cdc Dengue Real Time Rt-Pcr	Positive (DENV-1)	Positive (DENV-1)	Positive (DENV-1)	Positive (DENV-1)
Cytokine Profile (Single Analyte Quantitative Cytokine Elisa Qiagen, Usa)	Patient 1	Patient 2	Patient 3	Patient 4
IL-6	0	101.2pg/ml	101.2pg/ml	101.2pg/ml
IL-8	1121pg/ml	805.6pg/ml	566.7pg/ml	205.4pg/ml
IL-10	1007pg/ml	713.51pg/ml	677.51pg/ml	12.51pg/ml
TNF α	0	0	0	0
INF γ	0	190.91pg/ml	170.5pg/ml	33.9pg/ml
Patient 2	Acute Phase Cytokine Levels	Convalescence Phase Cytokine Levels		
IL-6	101.02	62.4		
IL-8	805.54	1360.29		
IL-10	713.51	0		
TNF α	0	0		
INF γ	190.91	0		

All the patients were referred from primary care centres where they were diagnosed with acute undifferentiated febrile illness. All the patients at the time of initial presentations did not present with typical features of dengue like rash, myalgia, retrorbital pain or bleeding manifestations. Gastrointestinal manifestations were predominantly seen in both the patients. Since there was an ongoing dengue epidemic the cases were suspected to be dengue and later confirmed by laboratory

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investigations All the patients were admitted to the general medical ward and were given symptomatic treatment for dengue. Routine investigations including platelet counts were monitored closely. One of the patients progressed to severe dengue with features of dengue shock he was admitted in the intensive care unit for further management. He was treated symptomatically with intravenous fluids, nutritional care, proton pump inhibitors and platelet supplementation as required.

Outcome and Follow-Up

One patient progressed to severe dengue with hepatic involvement, he subsequently developed multi organ failure and succumbed to death. Rest had persistent warning signs of dengue two units of platelets were transfused owing to the decreasing platelet counts. He had a gradual clinical improvement. All the hematological parameters were retested and were within normal range. Patient was discharged with the advice to continue plenty of fluid intake.

DISCUSSION

Determinants for development of severe dengue in certain patients are multifactorial. However, it is now established that one can progress to severe dengue irrespective of the serotype of the virus, whether the disease is primary or secondary. In our study both the patients were infected by DENV-1. Several studies have proven the role of inflammatory cytokines in severe dengue.[4] With this view; these two cases of dengue who initially came with similar complaints but later progressed to varying severity of dengue were taken under in this study. Elevation of IL-10 and IL-8 clinically corroborates with hepatitis and subsequent multi organ failure as reported in previous studies.[5] In the second case, the patient had grade IV thrombocytopenia and mildly raised liver enzymes which correlated with the raised IL-8, which significantly decreased during the convalescent phase. However, there was a persistent elevation of IL-8 which could be due to the presence of anti NS1. Since cytokines are being widely used in therapeutic and diagnostics of infectious diseases. Knowing the exact role of the cytokines will enable us to use cytokines as tool for identification of patient groups at risk to develop severe dengue.[6]

Learning Points/Take Home

- Patients with warning signs dengue can progress to severe dengue without typical bleeding manifestations
- Primary dengue cases can progress to severe dengue
- Real time RT-PCR for rapid detection of dengue viruses (1-4) will be useful in patients with warning signs dengue
- Cytokine profiling can aid in early identification of severe dengue thereby prevent the associated mortality and morbidity.

CONCLUSION

Patients with warning signs dengue can progress to severe dengue without typical bleeding manifestations

Primary dengue cases can progress to severe dengue

Real time RT-PCR for rapid detection of dengue viruses (1-4) will be useful in patients with warning signs dengue

Cytokine profiling can aid in early identification of severe dengue thereby prevent the associated mortality and morbidity.

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