INTERNATIONAL JOURNAL OF BIOASSAYS
ISSN: 2278-778X
CODEN: IJBNHY
ORIGINAL RESEARCH ARTICLE
OPEN ACCESS

A PROSPECTIVE OBSERVATIONAL STUDY OF CLINICAL PREDICTORS OF OUTCOME IN DENGUE IN CHILDREN

Sarada G, Suhasini M, Venkata Chetty A and G Sudhakar*
Department of Pediatrics, Government General Hospital, Kurnool Medical College, Kurnool, Andhra Pradesh, India.

Received for publication: May 21, 2015; **Accepted**: June 11, 2015

Abstract: In this Prospective Observational study during study period of one year, the incidence of severe dengue was 18% among children admitted with diagnosis of dengue fever. Nearly 40% children were of age 0-5 years. Case fatality rate in severe dengue was 5.5% .78% children responded either to crystalloids/colloids. Incidence of shock and bleeding at admission was significantly higher among children who died. Incidence of hepatic dysfunction and coagulopathy were higher and mean platelet count was lower in children who died compared to children who survived. Presence of shock, bleeding tendencies, coagulopathy at admission predict non response to fluids.

Key words: Dengue; Severe Dengue; Shock, Bleeds, Response to Therapy

INTRODUCTION

Dengue is the most common arthropod-borne viral (Arboviral) illness, transmitted by mosquitoes of the genus *Aedes,* which are widely distributed in subtropical and tropical areas of the world. Globally, 2.5-3 billion individuals live in approximately 112 countries that experience dengue transmission. Annually, approximately 50-100 million individuals are infected. Currently, dengue hemorrhagic fever is one of the leading causes of hospitalization and death in children in many Southeast Asian countries. Dengue fever has been reported from India over a long time, but dengue hemorrhagic fever was first reported in 1963 from Calcutta. Since then several outbreaks of dengue fever was reported from India with a major epidemic of dengue hemorrhagic fever that occurred in Delhi in 1996 when 10 252 cases and 423 deaths were reported. Cases have been reported from the neighboring states of Haryana, Punjab, Rajasthan, Uttar Pradesh and two southern and western states. DEN-2 was isolated during this epidemic and the proportion of DHF to DF was very high. The number of DF/DHF cases and deaths reported since the epidemic has been low till 2002 but again has risen in 2003. In 2005, both the reported dengue cases and deaths show threefold increase as compared to 2004. The case fatality has been above 1% for the last 10 years. However, the number of reported dengue cases and deaths are mainly from the capital city Delhi and the other states that have small outbreaks go unreported. In 2006 the number of cases reported as compared to 2005 shows some reduction whereas the Case fatality rate has remained above 1%. During 2007 (up to 19 June), 383 cases and 6 deaths have been reported from Kerala (188 cases); Gujarat (93); Maharashtra (15); Tamil Nadu (41); Karnataka (27); Haryana (5); Delhi (4); Rajasthan (4), Orissa (4), Chandigarh (1) and Uttar Pradesh.

***Corresponding Author:**
Dr. G. Sudhakar,
Professor Of Pediatrics,
Government General Hospital,
Kurnool Medical College,
Kurnool, Andhra Pradesh, India.

MATERIAL AND METHODS

Study objective: To study the clinical profile and predictors of mortality in children with severe dengue.

Place of study: Department of Pediatrics, Government General Hospital, Kurnool Medical College, Kurnool.

Time of study: June 2010 to May 2014

Type of study: Prospective observational study

Inclusion Criteria

Children with age less than 15 years, admitted to the pediatric department of government general hospital, Kurnool, with severe Dengue fever.

Criteria for severe dengue

1) Shock (DSS)
2) Fluid accumulation with respiratory distress
3) Severe bleeds
4) Severe organ involvement
   - LIVER : AST/ALT >300 IU
   - CNS : Impaired consciousness
   - HEART : Myocarditis / Cardiomyopathy
   - LUNGS : Acute Respiratory Distress Syndrome

Exclusion criteria

All children diagnosed with severe dengue but got transferred to other pediatric intensive care units for management were excluded from the study.

Methods

All children (age than 15 years) admitted to the paediatric department with fever for > 3days for screened for a diagnosis of Dengue fever. The screening included clinical examination for hepatomegaly, rash, signs of plasma leak and organ dysfunction. Baseline investigations included hematocrit, total and differential leucocyte count, platelet count, smear for malaria parasite and urine

exam for pus cells. X-ray chest, blood and urine culture, ultrasound abdomen, liver function tests, arterial blood gas, electrolytes, renal function tests were done when indicated. Whenever the clinical exam and lab investigations supported a possible diagnosis of dengue fever, Dengue Serology sent for the diagnosis of dengue fever. The diagnosis of dengue fever was defined as

Dengue classification

1. Non severe Dengue fever
    a. Probable Dengue
    b. Dengue with warning signs
2. Severe Dengue fever

Criteria for probable dengue

1. Live in / travel to Dengue endemic area
2. Fever and any two of the following
    i. Nausea and vomiting
    ii. Rash
    iii. Myalgias and arthralgias
    iv. Tourniquet test positive
    v. Leucopenia
    vi. LAB: Dengue serology IgG and IgM positivity
    vii. No signs of plasma leakage

Criteria for dengue with warning signs

1. Abdominal pain or tenderness
2. Persistent vomiting
3. Clinical fluid accumulation
4. Mucosal bleed
5. Lethargy and restlessness
6. Liver enlargement more than 2 cm
7. Lab: Increase in haematocrit with concurrent fall in platelet count

In children with dengue fever, if the criteria for severe dengue fever were met, he or she was included in the study after obtaining an informed consent from the parents.

All children with severe dengue were transferred to the Pediatric intensive care unit and monitored for vital signs continuously, hematocrit and platelet counts twice daily and other investigations as and when needed. The fluid management was based on the WHO protocol.

Children were discharged home when the vitals were normal, accepting oral feeds, had platelet counts 1, 00,000/mm^3 and afebrile. All discharged infants for reviewed for follow up at day 7 of discharge. The outcome was recorded as mortality and discharged home.

In all children included in the study, the clinical profile, laboratory investigations, response to fluid therapy and outcome was prospectively recorded in predesigned proforma. The data collected included

1. Age in years
2. Sex
3. Place of residence
4. Day of fever at admission
5. Presence of rash
6. Hepatomegaly in cms below costal margin at admission
7. Shock at admission (Blood pressure less than < 5th percentile for the age)
8. Systolic BP at admission
9. Diastolic BP at admission
10. Platelet count at admission
11. SGOT and SGPT at admission
12. Gall bladder edema
13. Pleural effusion diagnosed on ultrasonography
14. Ascites diagnosed on ultrasonography
15. Chest x ray showing acute respiratory distress syndrome
16. CXR showing pulmonary edema
17. Use of IVIG
18. Mortality

Outcome:

Mortality is the primary outcome of this study.

Statistics

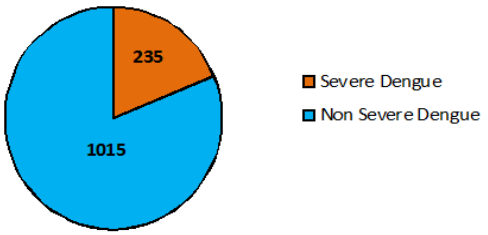
The clinical data and complications of severe dengue fever presented as percentages or proportions. All clinical and lab variable were compared between those children who were discharged home and those who died in the hospital. Categorical variables were compared with chi-square test and continuous variables with student t test or Mann-Whitney U test as appropriated. To find an independent association logistic regression analysis was done with mortality as the dependent variable and variables significant on univariate analysis as predictor/independent variables.

Sample size

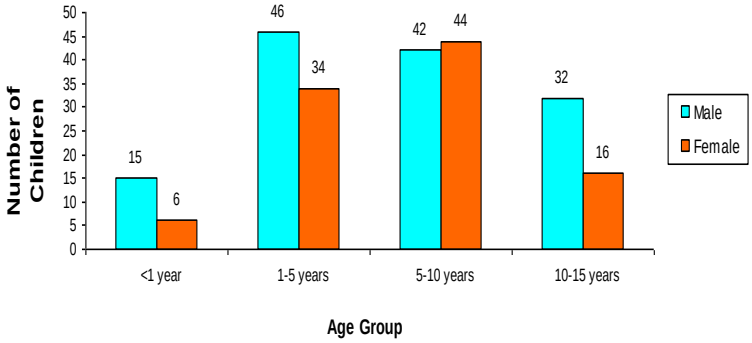
No appropriate sample size was estimated for this prospective observational study.

RESULTS

Number of Children in relation to severity of Dengue Fever

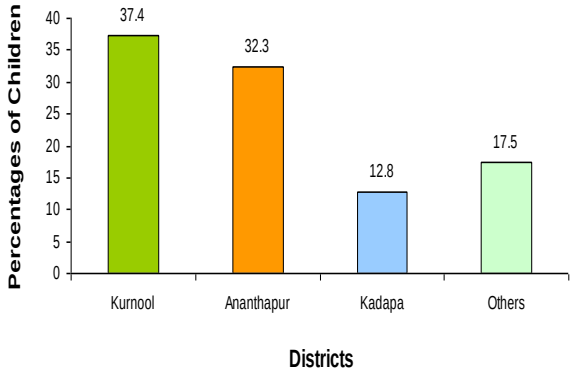


During the study period from June 2010 to May 2011, out of 1250 children diagnosed with dengue fever, 235 children were qualified for diagnosis of severe dengue and those were enrolled in the study.

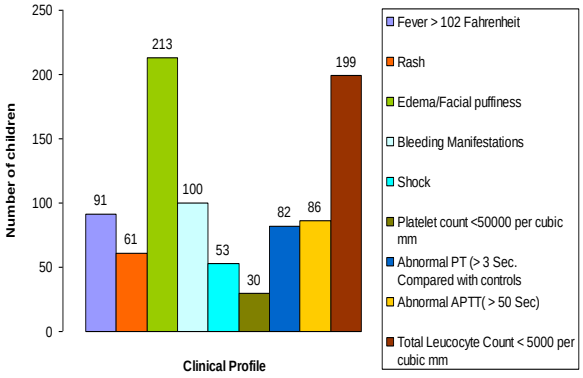


The mean age of the children enrolled in the study was 6.43±0.46 days, 21(8.9%) were infants, 80(34%) children were in the age group 1 to 5 yrs, 98(42%) were in the age group 5 to 10 yrs and the rest 57 (24 %) had an age more than 10yrs. 135 children (57.4%) were males. Majority of the children reported to us were from the districts of Kurnool (37.4%), Anantapur (32.3%) and Kadapa (12.8%).

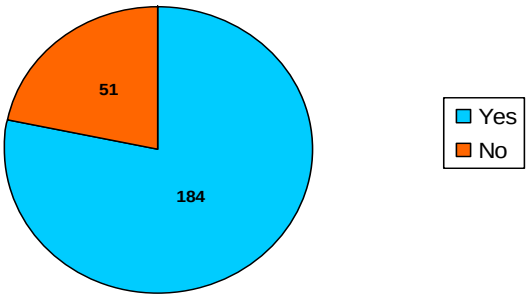
192 children had fever at admission; the mean number of days from onset of fever to admission was 4.5±1.7 days. 101 children had fever ranging from 100 to 102° F and 91 children had fever >102°F at admission. 61 (26%) children presented with rash, 213 (90.6%) had edema/facial puffiness, 100(42.6%) had 1 or other bleeding manifestations (petechiae, malena, GI bleed and hematuria) and the rest 135(57%) had no bleeding at admission. 53(22.6%) children presented with shock.



Mean platelet count at admission was 83,200/mm^3 and the platelet count ranged from 18,000 /mm^3 to 1,46,000/mm^3. 6 (2.6%) children had platelet count <30,000/mm^3 at admission while 24(10.2%) children had platelet counts between 30,000 to 50,000/mm^3 at admission. 82 (35%) children had abnormal PT (>3seconds compared with the control), 86 (37%) children had abnormal APTT (>50seconds) and 199(84.7%) children had total leucocyte count <5000/mm^3.

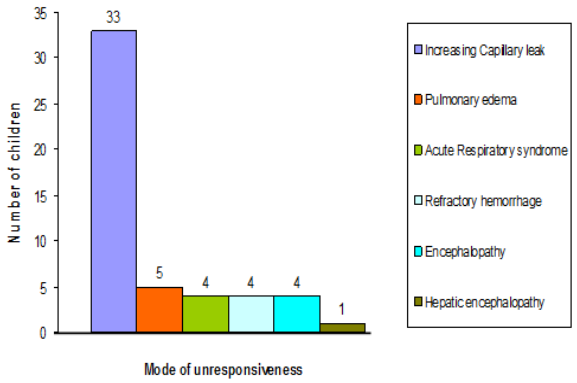


Response to Crystalloids and Colloids



Of children with severe dengue, 51 children (21.70%) did not respond to crystalloids/colloids.13 children (5.53%) died in the hospital due to various complication of severe dengue fever.

Of 235 children with severe dengue, 33(19.6%) had capillary leak, 5(2.1%) had pulmonary edema on chest x-ray, 4 each had acute respiratory distress syndrome (ARDS), refractory hemorrhage and encephalopathy, one child presented with hepatic encephalopathy. None of the children had cardiomyopathy as presentation during study.



Of 235 children, 184(78.3%) responded to fluid therapy (either crystalloids/colloids) meaning blood

pressure, heart rate and pulse volume normalized and there was drop in packed cell volume (PCV) by 15%. 51(21.70%) children did not show improvement in either heart rate/blood pressure/fall in PCV with fluid therapy. Children who responded to fluid therapy were compared with those who did not respond to fluids. The mean age of child {6.32±3.4 years Vs 6.46±4.2 years, p=0.83}, proportion of males {n=25(49%) Vs n=110(59.8%) P=0.169}, presence of rash at the time of admission, {n=15(29.4%)Vs n=46(25.0%) P=0.525} were similar between non responders and responders respectively. More children in the group with fluid response had fever at admission, the time from onset of fever to admission was significantly higher in non-responders {n=163(88.6%) Vs n=29(56.8%) P= <0.001}, {4.9±2.3 Vs 4.4±1.4, P=0.047}. Presence of clinical features like facial puffiness/ edema/ ascites were significantly higher in non-responders and also incidence of shock at admission higher in non-responders. {n=50(98%) Vs n=163(88.6%), P=0.040}, {n=44(86.3%) Vs n=36(19.6%), P= <0.001}, {n=43(84.3%) Vs n=10(5.4%), P=<0.001}. Liver size was higher and systolic and diastolic blood pressures were lower in children who did not respond to fluid therapy {n=5.93±1.058 Vs n=4.15±0.74, P= <0.001}, {n=82.27±11.7 Vs n=96.98±14.05, P=0.001}, {n=52.16±9.13 Vs n=57.32±10.35, P=0.002}. Incidence of bleeding manifestations was lower in those children who responded to fluid therapy {n=116(63%) Vs n=19(37.3%), P=0.001}. Mean platelet count was significantly lower in non-responder group {57,100 ± 23,722 /mm^3 Vs 90,500 ± 25766/mm^3, P= <0.001}. Mean SGOT/SGPT was significantly lower in non-responder group {131.45±67 Vs 67.96±86.25±34, P= <0.001}, {198.55±155 Vs 86.25±34, P= <0.001}. Pro portion of children with abnormal PT, APTT and total leukocyte count <5000/mm^3 significantly higher in non-responders {n=45(88%) Vs n=37(20%), P= <0.001}, {n=45(88%) vs. n=41(22%), p= <0.001}, {n=48(94%) Vs n=151(82%), P=0.0046}.

Mean age of the child {6.23±3.5years vs 6.44±4.1years, p=0.85}, proportion of the males,{n=6(46.2%) vs. n=129(58.1%), p=0.397}, presence of rash at admission {n=4(30.8%) vs. n=57(25.7%), p=0.684} were similar in both the children who survived and those who died.

Most of the children who survived survival had fever at admission while the time from onset of fever to admission was significantly higher in children who were expired. {n=185(83.3%) Vs n= 7(53.9%), P=0.026},{5.38±2.8 Vs 4.46±1.6, P=0.052}.

All children who expired had facial puffiness/edema/ascites and incidence of shock at admission was higher in the children who expired. {n=13(100%) vs n=200(90.1%), P=0.233},{n=13(100%) Vs n=67(30.2%), P= <0.001},{n=13(100%) Vs n= 40(18%), P= <0.001}.

Liver size was higher and systolic and diastolic Blood pressures were lower in children who died of severe dengue fever. {6.54±0.6 Vs 4.42±1.00, P= <0.001}, {78.45±7.00 Vs 94.65±14.71, P= <0.001},{50.18±9.05 Vs 56.54±10.3,P=0.046}.
Incidence of bleeding manifestations was lower in children who survived {n=130(58.6%) Vs n=5(38.5%), P=0.154}

Mean platelet count was significantly lower in children who died {41,500 ± 18,186 /mm^3 vs. 85,700 ± 27,436 /mm^3, p= <0.001}.

Mean SGOT and mean SGPT was significantly higher in children who expired. {308.85±246 Vs 99.01±54, P= $^{<0}$.001}, {159.46±77 Vs 77.18±4^2, P= <0.001}.

All children who expired had abnormal PT and APTT with total leucocyte count <5000. {n=13(100%) vs n=69(31%), p= <0.001}, {n=13(100%) Vs n=73(33%), p= <0.001}, {n=13(100%) vs n=186(84%), p=0.22}

On logistic regression, the factors independently associated with no response to fluid therapy in children with dengue therapy were shock, presence of bleeding tendency and abnormal PT. As the incidence of outcome i.e. death was very low, we could not do regression analysis for this outcome

DISCUSSION

In this Prospective Observational study during study period of one year, the incidence of severe dengue was 18% among children admitted with diagnosis of dengue fever. Nearly 40% children were of age 0-5 years. Case fatality rate in severe dengue was 5.5% .78% children responded either to crystalloids/colloids. Similar to our study, in a study by Kamat *et al.*, from Chennai, incidence of severe dengue requiring PICU admission was 12.7% and case fatality rate was 8.3%.In a study from Pakistan, the incidence of severe dengue was 13.6% and overall mortality was 2.7%.In our study, there was a delay in reporting to hospital by 24hrs in children who died. Incidence of shock and bleeding at admission was significantly higher among children who died. Incidence of hepatic dysfunction and coagulopathy were higher and mean platelet count was lower in children who died compared to children who survived.

Similar to our study, in the report from Pakistan, altered liver enzymes, presence of bleeding and shock at admission was significantly altered with

mortality. We did not do logistic regression analysis as the outcome of interest (ie. death) was very low.

In a study by Agarwal *et al.,* from New Delhi, the mortality was 6% in children with dengue hemorrhagic fever and dengue shock syndrome, similar to this study incidence of severe dengue was 8.9% in children.

None of the previous studies reported predictors of non-responsiveness to fluids.in our study on logistic regression, the factors independently associated with non-responsiveness to fluids were presence of Shock, hemorrhagic manifestations and coagulopathy at admission. Children with dengue fever should be managed early with fluids and one needs to develop simple algorithm for early referral of children who may develop these complications. Once shock sets in, the management is difficult and case fatality rate rises.

CONCLUSION

Severe dengue occurs in 18.8% of children with dengue fever, case fatality rate is 5.5%.Presence of shock, bleeding tendencies, coagulopathy at admission predict non response to fluids.

This is the large study involving 235 children with severe dengue. There was uniformity in management of severe dengue throughout study period. All cases managed by the same PICU team and using WHO protocol. This is the first study look at predictors of non-responsiveness to fluids.

REFERENCES

1. WHO Dengue guidelines for diagnosis, treatment, prevention and control. New edition 2009
2. Halstead SB. Dengue. Lancet 2007; 370:1644-52.
3. Kurane I. Dengue hemorrhagic fever with special emphasis on immunopathogenesis. Comp Immunol Microbiol Infect Dis 2007; 30:329-40.
4. Littaua R, Kurane I, Ennis FA. Human IgG Fc receptor II mediates antibody-dependent enhancement of Dengue virus infection. J Immunol 1990;144:3183-6.
5. Ostronoff M, Ostronoff F, Florêncio R, Florêncio M, Domingues MC, Calixto R, *et al.,* Serious thrombocytopenia due to Dengue hemorrhagic fever treated with high dosages of immunoglobulin. Clin Infect Dis 2003;36:1623-4.
6. Alejandria M. Dengue fever. Clin Evid 2005:887-95.
7. Rajapakse S. Intravenous immunoglobulins in the treatment of Dengue illness. Trans R Soc Trop Med Hyg 2009; 103:867-70.

CITE THIS ARTICLE AS:
Sarada G, Suhasini M, Venkata Chetty A and G Sudhakar, A Prospective Observational Study of Clinical Predictors of Outcome in Dengue in Children, International Journal of Bioassays, 2015, 4 (07), 4050-4054.

Source of support: Nil
Conflict of interest: None Declared