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Original Research Article

Biochemical parameters (lactate dehydrogenase, serum albumin) as early predictor of severe dengue

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ABSTRACT

Background: Dengue fever (DF) is the arboviral infection with the largest incidence worldwide. Clinical expression of dengue virus infection varies from no symptoms to severe dengue with shock. It is the most rapidly spreading vector borne disease in the world. Nearly 100 million cases of Dengue fever and between 250,000 and 500,000 cases of severe dengue are annually reported to the WHO. The objective of this study was to study aims at determining the LDH and serum albumin levels as early parameter to predict the severity of Dengue illness.
Methods: A observational clinical study conducted at K.I.M.S hospital, Bangalore, Karnataka, a tertiary care hospital. Children admitted in KIMS Hospital, Bangalore, Karnataka, a tertiary care hospital, Serum LDH and serum albumin levels are measured using the blood sample taken on the 3rd day of fever after confirmation of dengue fever (NS1 Ag- positive).
Results: Study enrolled 150 patients with confirmed infection of Dengue virus who were admitted to paediatric unit between July 2014 and December 2016. Serum samples taken 72-96 hours within onset of fever were used for biochemical tests. Of 150 patients, 40 developed Severe Dengue (SD). Cases of SD had higher levels of lactate dehydrogenase (LDH) and low levels of serum albumin. Multivariate analysis showed that early alterations of LDH levels i.e. Out of 40 patients who developed severe dengue, 37 patients i.e. 92.7% had raised levels of LDH with levels more than >600 IU and<3 levels of serum albumin 13 patients i.e 32.5% of severe dengue cases with P value of < 0.001, which showed significant association.
Conclusions: Early alterations of biochemical parameter like LDH and serum albumin can predict Severe Dengue in patients with acute dengue illness.

Keywords: DF, LDH, SD

INTRODUCTION

Dengue fever is the arboviral infection with the largest incidence worldwide.[1] Clinical expression of dengue virus infection varies from no symptoms to severe dengue with shock. Nearly 100 million cases of dengue fever and between 250,000 and 500,000 cases of severe dengue are annually reported to the World Health Organization.[2,3] Severe dengue is characterized by thrombocytopenia, spontaneous haemorrhages, and gradual plasma leakage that can lead to shock.[4] Despite its clinical variability, the acute phase of dengue begins with fever that is indistinguishable from the initial phase of other acute febrile infectious diseases.

Thus, acute dengue infection is often unrecognized until the appearance of the more severe forms of the disease.[1,2,4] This non-specificity of clinical features leads to inadequate or late treatment of a potentially lethal medical condition. There is direct and indirect evidence of biochemical and radiological alterations related to severity of dengue.[5,6]

- Studies have reported that those patients with severe dengue have increased levels of LDH and decreased levels of serum albumin.

However, these potential biochemical markers have not been evaluated prospectively in early stages of dengue and their utility as predictors of dengue children progressing to severe dengue have not been studied previously in our part of the country.

METHODS

A observational clinial 'Study of biochemical alteration as predictors of severe dengue'conducted at K.I.M.S Hospital, Bangalore, Karnataka, a tertiary care hospital. In study children admitted in KIMS Hospital, Bangalore, Karnataka, a tertiary care hospital, serum LDH and serum albumin levels are measured using the blood sample taken on the 3rd day of fever after confirmation of dengue fever (NS1 Ag- positive).

Inclusion criteria

- Children coming with 3 days of fever or in febrile phase of dengue fever
- Children coming with any complications of dengue fever i.e severe dengue

Exclusion criteria

- Neonates
- Children coming in afebrile phase of dengue fever
- Children with history of hepatic/cardiac/ hematological disorders/malnutrition.

Sample size where selected 150 samples.

All children coming with 3 days of fever or in febrile phase of dengue fever/children coming with any complications of dengue fever i.e severe dengue.

Method of collection of data

- Informed and written consent is obtained from the parent/guardian of the child
- Weight and height are recorded for all children to assess the nutritional status and classified into mild, moderate malnutrition using IAP classification
- The following investigations are done in all cases: Hemoglobin (Hb%), Packed cell volume (PCV%), platelet count, dengue serology, lactate dehydrogenase (LDH) and serum albumin.

Results were tabulated and statistical analysis was performed using appropriate tests and functions.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, assumptions;

- Dependent variables should be normally distributed
- Samples drawn from the population should be random, Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.

Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for Qualitative data analysis.[7-10]

Significant figures

- + Suggestive significance (P value: $0.05<P<0.10$)
- Moderately significant (P value:$0.01<P\leq0.05$)
- ** Strongly significant (P value: $P\leq0.01$)

Statistical software

The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

150 children who met with inclusion criteria were enrolled in to the study. Statistical analysis was done and results are presented as follows.

- Age
- Sex
- Presenting complaints
- Nutrition
- Dengue serology
- LDH levels
- Serum albumin
- Outcomes.

Age

Table 1: Age distribution among cases.

Age in years	No. of patients	%
<2	10	6.7
2-10	72	48.0
11-20	68	45.3
Total	**150**	**100.0**

Mean ± SD: 9.58±4.59.

In this study, among 150 cases, 40 cases went to severe dengue out of which 17 (42.5%) were in age group of 2 years to 10 years and 18 (45%) were from 11 years to 18 years.

Table 2: Correlation between age and severe dengue.

Age in years	Outcome		Total
	Improved	Severe dengue	
<2	5 (4.5%)	5 (12.5%)	10 (6.7%)
2-10	55 (50%)	17 (42.5%)	72 (48%)
11-20	50 (45.5%)	18 (45%)	68 (45.3%)
Total	**110 (100%)**	**40 (100%)**	**150 (100%)**

P = 0.209; Not significant; Chi-Square test.

No significant association of age with severe dengue was seen.

Sex

In this study, among 150 cases, males were predominant - 92 (61.3%) cases, females comprised of 58 (38.7%).

Table 3: Gender distribution among cases.

Gender	No. of patients	%
Female	58	38.7
Male	92	61.3
Total	**150**	**100.0**

Table 4: Correlation between gender and severe dengue.

Gender	Outcome		Total
	Improved	Severe dengue	
Female	40 (36.4%)	18 (45%)	58 (38.7%)
Male	70 (63.6%)	22 (55%)	92 (61.3%)
Total	**110 (100%)**	**40 (100%)**	**150 (100%)**

No significant correlation was found between sex of the child and outcome of the disease.

Presenting complaints

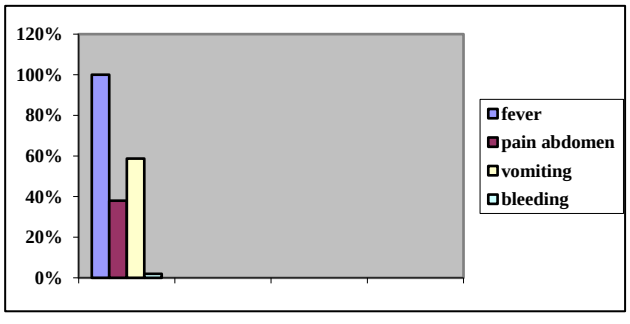

Figure 1: Presenting complaints.

Among the 150 cases, WHO criteria were used to define a case. Fever was seen in 100% of the subjects, pain abdomen in 38% of patients, vomiting in 58.7% patients and bleeding in 2% of patients.

Table 5: Fever distribution among cases.

Fever (days)	Gender		Total
	Female	Male	
1	0 (0%)	1 (1.1%)	1 (0.7%)
2	8 (13.8%)	9 (9.8%)	17 (11.3%)
3	25 (43.1%)	51 (55.4%)	76 (50.7%)
4	25 (43.1%)	31 (33.7%)	56 (37.3%)
Total	58 (100%)	92 (100%)	150 (100%)

All patients presented to us with complaints of fever varying in number of days (1-4 days) and other complaints like pain abdomen, vomiting and bleeding.

Most cases presented with complaints of fever for 3 days.

Table 6: Correlation with fever days and outcome.

Fever (days)	Outcome		Total
	Improved	Severe dengue	
1	1 (0.9%)	0 (0%)	1 (0.7%)
2	13 (11.8%)	4 (10%)	17 (11.3%)
3	52 (47.3%)	24 (60%)	76 (50.7%)
4	44 (40%)	12 (30%)	56 (37.3%)
Total	**110 (100%)**	**40 (100%)**	**150 (100%)**

P = 0.585; Not significant; Chi-Square test.

No significant correlation was seen with number of days of fever and severe dengue.

Table 7: Pain abdomen incidence.

Pain abdomen	Gender		Total (n = 150)
	Female (n = 58)	Male (n = 92)	
No	36 (62.1%)	57 (62%)	93 (62%)
Yes	22 (37.9%)	35 (38%)	57 (38%)
1	10 (17.2%)	24 (26.1%)	34 (22.7%)
2	11 (19%)	10 (10.9%)	21 (14%)
3	1 (1.7%)	1 (1.1%)	2 (1.3%)

Table 8: Correlation of pain abdomen days with outcome.

Pain abdomen	Outcome		Total
	Improved	Severe dengue	
No	78 (70.9%)	15 (37.5%)	93 (62%)
Yes	32 (29.1%)	2 5(62.5%)	57 (38%)
Total	**110 (100%)**	**40 (100%)**	**150 (100%)**

P<0.001**; Significant; Chi-Square test.

Complaints of pain abdomen was associated with increased risk of severe dengue.

Table 9: Distribution of vomiting in children.

Vomiting	Gender		Total (n = 150)
	Female (n = 58)	Male (n = 92)	
No	26 (44.8%)	36 (39.1%)	62 (41.3%)
Yes	32 (55.2%)	56 (60.9%)	88 (58.7%)
1	19 (32.8%)	35 (38%)	54 (36%)
2	11 (19%)	21 (22.8%)	32 (21.3%)
3	2 (3.4%)	0 (0%)	2 (1.3%)

54% of children presented with complaints of vomiting only for 1 day with total of incidence of vomiting being 58.7%, whereas no vomiting was seen in 41.3% of children.

Table 10: Incidence of bleeding in children.

Bleeding	Gender		Total (n = 150)
	Female (n = 58)	Male (n = 92)	
No	55 (94.8%)	92 (100%)	147 (98%)
Yes	3 (5.2%)	0 (0%)	3 (2%)
1	3 (5.2%)	0 (0%)	3 (2%)

Bleeding was seen in only 3 children, only 2% of cases and all of them were female children.

Table 11: Vomiting /bleeding incidence of patients studied in relation to outcome.

	Outcome		Total (n = 150)	P value
	Improved (n = 110)	Severe dengue (n = 40)		
Vomiting	60 (54.5%)	28 (70%)	88 (58.7%)	0.089+
Bleeding	0 (0%)	3 (7.5%)	3 (2%)	0.004 **

by Chi-Square test/Fisher Exact test.

Table 12: LDH distribution in patients.

LDH	Gender		Total
	Female	Male	
<300	5 (8.6%)	18 (19.6%)	23 (15.3%)
300-600	39 (67.2%)	55 (59.8%)	94 (62.7%)
>600	14 (24.1%)	19 (20.7%)	33 (22%)
Total	**58 (100%)**	**92 (100%)**	**150 (100%)**

62.7% of cases were seen with LDH of 300-600IU/L

Bleeding complaints was associated with higher incidence of severe dengue as compared to vomiting, which has suggestive significance for leading to severe dengue.

All cases were NS1Ag positive with nutrition being normal.

Increased levels of LDH was associated with increased risk of severe dengue.

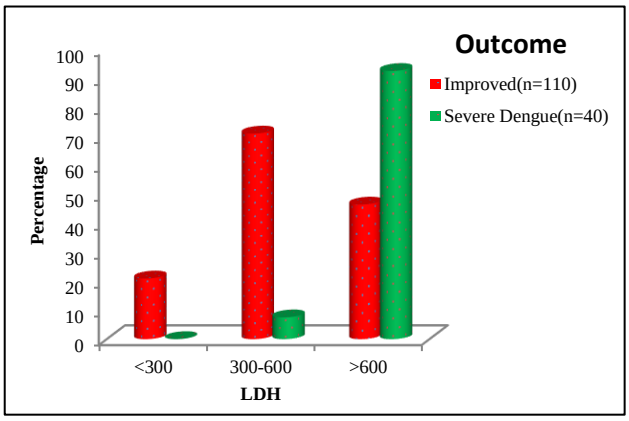

Figure 2: Association of LDH with severe dengue.

Table 14: Distribution of serum albumin in children.

Serum albumin	Gender		Total
	Female	Male	
<2.5	2 (3.4%)	1 (1.1%)	3 (2%)
2.5-3.5	28 (48.3%)	36 (39.1%)	64 (42.7%)
>3.5	28 (48.3%)	55 (59.8%)	83 (55.3%)
Total	**58 (100%)**	**92 (100%)**	**150 (100%)**

Most cases had serum albumin levels above 3.5g/dl i.e 55.3%.

Level of serum albumin <3 was associated with increased risk of severe dengue.

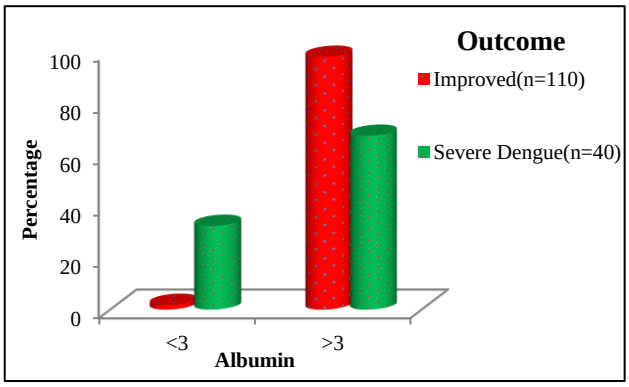

Figure 3: Association of serum albumin with severe dengue.

Table 15: Association of study variables in relation to outcome.

Variables	Outcome		Total (n = 150)	P value
	Improved (n = 110)	Severe dengue (n = 40)		
LDH				
<300	23 (20.9%)	0 (0%)	23 (15.3%)	<0.001**
300-600	78 (70.9%)	3 (7.5%)	39 (26%)	
>600	51 (46.4%)	37 (92.5%)	88 (58.7%)	
CPKMB				
<50	93 (84.5%)	18 (45%)	111 (74%)	<0.001**
50-100	17 (15.5%)	17 (42.5%)	34 (22.7%)	
>100	0 (0%)	5 (12.5%)	5 (3.3%)	

Variable was estimated with Chi-square test and was significantly positive for association with severe dengue for early prediction.

DISCUSSION

Dengue fever is the most important arboviral infection of humans and has become a major global public health problem. It is one of the most important tropical infectious disease in the world.

In India, epidemics are becoming more frequent. Involvement of younger age group and increasing in the frequency of epidemics are indicators of higher incidence of infection. Classical dengue fever is an acute febrile illness but in a small percentage of Dengue infection, a more severe form of disease known as DHF occurs. Early recognition and meticulous management are very important to save precious lives from this killer disease.

Incidence

In the present study of 150 confirmed dengue cases, 40 cases i.e 26.6% of children had severe dengue (SD) and 73.33% had dengue fever.

Age distribution

Although high incidence of degree has been described in children, very few studies have been exclusively studied on them. The 2-10 year age group and 11-18 age group which had 72 (48%)cases and 68 (45.3%) cases respectively, formed the major number of cases.[4]

The 2-10 years age group formed 48% of the study which correlated with the previous studies.[11]

Among the subgroup, there is a tendency for SD to occur at younger age. However previous studies have not noted any difference in age between dengue with or without shock. The youngest child in the present study was 8 months old.[12] Other studies with age predominance between 5-11 years are as follows.

Gender distribution

The incidence of male children that were affected is slightly more in our study, the ratio being 1.58:1. Similar observation were made by others also showed increased preponderance among boys as in WHO study in 1999 due to increased outdoor activities of male children.[13-18]

Symptomatology

In the present study fever (100%) was the predominant symptoms followed by vomiting (58.5%), abdominal pain (38%), bleeding (2%) of cases.

The following pattern of symptoms have been observed in other studies.[11,19-23]

Investigations

Lactate dehydrogenase

Out of 40 cases of SD, 33 patients had serum LDH >600 i.e. 82.5% of total SD cases and formed 22% of total cases.

Out of 150 cases, 94 cases i.e. 62.7% had serum LDH levels 300-600.

Serum LDH was a helpful predictive marker.[24,25]

Serum albumin

Out of 150 cases, 15 cases had serum albumin levels <3 i.e. 10%. Out of 40 SD cases, 13(32.5%) had serum albumin <3.[26]

Plasma leakage, which indicates that dengue causes hypoalbuminemia, is an indicator of severity. In our study, albuminemia <3 g/dl was associated with higher incidence of SD. Usually high values of albuminemia may reflect the integrity of the vascular endothelium, whereas albumin levels less than 3 g/dl may be an early indicator of vascular permeability alteration. Therefore,

this parameter may be an early indicator of plasma leakage and a useful prognostic marker.[27]

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ministry of Tourism Indian Tourism Statistics. 2013. Available at http://tourism.gov.in/market-research-and-statistics. Accessed on August 2016.
2. World Bank India Overview. 2013. Available at https://openknowledge.worldbank.org/bitstream/handle/10986/16091/9780821399378.pdf. Accessed on August 2016.
3. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet. 1998;352:971-7.
4. Bagchi S. Dengue bites India. CMAJ. 2009;180:E7.
5. Kakkar M. Dengue fever is massively under-reported in India, hampering our response. BMJ. 2012;345:e8574.
6. Yip WCL. Dengue haemorrhagic fever: current approaches to management. Medical Progress. 1980;7:13.
7. Centers for disease control and prevention (CDC): Ongoing dengue epidemic-Angola. Morb Mortal Wkly Rep. 2013;62:504-8.
8. de Alwis R, Smith SA, Olivarez NP, Messer WB, Huynh JP, Wahala WM, et al: Identification of human neutralizing antibodies that bind to complex epitopes on dengue virions, Proc Natl Acad Sci USA. 2012;109:7439-44.
9. Durbin AP, Kirkpatrick BD, Pierce KK. A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naive adults: a randomized, double-blind clinical trial. J Infect Dis. 2013;207:957-65.
10. Rosner B. Fundamentals of biostatistics, 5th Edition, Duxbury; 2000:80-240.
11. Riffenburg RH. Statistics in Medicine, second edition, Academic press; 2005:85-125.
12. Chye JK, Lim CT, Ng KB, Lim JMH, George R, Lam SK, et al. Vertical transmission of dengue. Clin Inf Dis. 1997;25:1374-7.
13. Liu CC, Huang KJ, Lin YS, Yeh TM, Liu HS, Lei HY, et al. Transient CD4/CD8 ratio inversion and aberrant immune activation during dengue virus infection. J Med Virol, 2002;68(2):241-52.
14. Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. Am J Trop Med Hyg, 1998;38:172-80.
15. Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health. 2007;12(9):1087-95.
16. Chakravarthi A, Kumaria R. Circulating levels of TNF-alpha in patients with dengue and dengue hemorrhagic fever during an outbreak. Indian J Med Res. 2006;123:25-30.
17. Ibrahim NM Cehong. Dengue hemorrhagic fever at Kuala Lumpur hospital; Retrospective study of 102 cases. Br J Clin Pract. 1995;49:189-91.
18. Nimmannitya S. Dengue and chikungunya virus infection in man in Thailand, 1962−64. Observations on hospitalized patients with haemorrhagic fever. Am J Trop Med Hyg. 1969;18(6):954-71.
19. Dengue: Clinical and public health aspects-transmission of dengue virus by Aedes aegypti. Centre Dis Cont. 1998:435-36.
20. Phase III trial to evaluate efficacy and safety of a dengue 1,2,3,4 (attenuated) vaccine 91. efficacy, safety and immunogenicity of Takeda's Tetravalent Dengue Vaccine (TDV) in Healthy Children (TIDES). Tetravalent Immunization against Dengue Efficacy Study. 2016.
21. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated). World Health Organization, Geneva, Switzerland; 2013.
22. Capeding MR. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebocontrolled trial. Lancet. 2014;384(9951):1358-65.
23. Sangkawahibha N, Rojanasuphot S, Ahandrik S. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. Am J Epidemiol. 1984;120:653-69.
24. Gubler DJ. Aedes aegypti and Aedes aegypti bone disease control in the 1990s. Top down or bottom up? Charles Franklin Craig Lecture. Am J Trop Med Hyg. 1989; 40:571-8.
25. Ayyub M, Khazindar AM, Lubbad EH, Barlas S, Alfi AY, Al-Ukayli S. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia. 2006;18(2):9-13.
26. Biochemical Alterations as Markers of Dengue Hemorrhagic Fever. Luis Angel Villar-Centeno, Fredi Alexander Díaz-Quijano, and Ruth Aralí Martínez-Vega School of Medicine, and Centro de Investigaciones Epidemiológicas, Universidad Industrial de Santander, Bucaramanga, Colombia. Am J Trop Med Hyg. 2008;78(3):370-4.
27. Sunder Rao PSS, Richard J. An introduction to biostatistics, a manual for students in health sciences, New Delhi: Prentice hall of India. 4th edition; 2006:86-160.

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