Comparison of Clinical and Laboratory Parameters between Chickungunya and Dengue: Are Liver Enzymes Reliable Indicators in These Infections?

Authors
Dr Hariharan Munganda, Dr Ajit Thakur, Dr Rakesh Kumar, Dr Sandip Bhattacharya, Dr Uma Rani
Asian Institute of Medical Sciences, Faridabad, Haryana, India - 121001

INTRODUCTION
Dengue and chikungunya are vector borne diseases sharing not only the season of epidemic but also the clinical features.
At times diagnosis is at stake owing to unavailability of specific test and targeted treatment is different for the two diseases as long duration is required in definitive testing.
It is important to differentiate between them during their first presentation with routinely available diagnostic tests with shorter turnaround time.
The need becomes more in case of dengue in view of possible complications such as dengue hemorrhagic fever and dengue shock syndrome.

AIMS AND OBJECTIVES
The aim of the study is to compare various clinical and laboratory findings between subjects with dengue fever (DF) and Chickungunya fever (CF) and to search for a routinely done investigation which can help to differentiate between the both.
The objective of this review is to provide physicians in general practice with a guide to interpreting liver enzyme alterations in chikungunya.

MATERIALS AND METHODS
Type of study: Hospital based observational cohort study
Data Collection: Prospective
Place of study: Asian institute of medical sciences, Faridabad, New Delhi, India
Cohort: Subjects presenting to the medicine and paediatric OPD & IPD with fever were screened, their thorough clinical history was taken and routine laboratory investigations were performed.
Groups: Based on results of chikungunya RTPCR and dengue serology subjects study subjects were diagnosed and classified in two groups
Dengue Fever: 25 subjects
Chickungunya fever: 27 subjects
Other routine investigations including CBC, LFT, KFT, PT, INR, P. SMEAR, USG ABDOMEN, CXR, ECG, 2D ECHO etc., were performed.
Clinical features and laboratory investigations were compared between the two groups using Chi square/ Fischers exact test (Frequency data) and student’s unpaired t test (categorical data).
ROC curve was plotted to check diagnostic significance of investigations for dengue fever
RESULTS

Table 1 General characteristics of study subjects:

| Characteristics | DIAGNOSIS          | N  | Mean  | Std. Deviation | Std. Error Mean | t     | Sig. (2-tailed) |
|-----------------|--------------------|----|-------|----------------|-----------------|-------|----------------|
| AGE (YEARS)     | Dengue fever       | 25 | 18.63 | 19.31          | 3.85            | -4.88 | 0.00           |
| BMI (Kg/m^2)    | Dengue fever       | 27 | 22.53 | 2.62           | 0.52            | -12.39| 0.00           |
| GENDER          | Female             | 10 | 17    | 32             | 1.00            |       |
| DIET            | Male               | 15 | 11    | 23             |                 |       |
| TAB HEPTRAL     | NONVEG             | 13 | 15    | 26             | 0.780           |       |
| ALCOHOL INTAKE  | GIVEN              | 7  | 8     | 15             |                 |       |
|                | NOTGIVEN           | 18 | 19    | 37             | 1.00            |       |
|                | NO                 | 25 | 24    | 49             |                 |       |
|                | YES                | 0  | 3     | 3              | 0.000           |       |

While the two groups were found to be sex matched (p=0.82), mean age was found to be significantly lower in DF.

Further myalgia and arthralgia was found to be significantly higher in CF while frequency of fever, abdominal pain, nausea, vomiting, respiratory distress was found to be higher in DF.

Laboratory investigations in study subjects

| Characteristics | DIAGNOSIS          | N  | Mean     | S.D.   | Std. Error Mean | t     | P value  |
|-----------------|--------------------|----|----------|--------|-----------------|-------|----------|
| PLATELET (mm^3)| Dengue fever       | 25 | 101120.00| 104302.00| 20800.43   | -2.39 | 0.02     |
|                | Chikungunya fever  | 27 | 160670.00| 74277.03| 14294.62   |       |          |
| AST (IU/L)     | Dengue fever       | 25 | 203.12   | 232.90  | 46.58        | 3.49  | <0.0001  |
|                | Chikungunya fever  | 27 | 45.89    | 25.19   | 4.85         |       |          |
| ALT (IU/L)     | Dengue fever       | 25 | 94.16    | 78.53   | 15.71        |       |          |
|                | Chikungunya fever  | 27 | 48.15    | 28.87   | 5.56         | 2.76  | 0.01     |
| AST AFTER 1 WEEK (IU/L)| Dengue fever | 25 | 106.84 | 90.18 | 18.04 | 3.30 | <0.0001 |
|                | Chikungunya fever  | 27 | 48.11   | 20.58   | 3.96         |       |          |
| AST ON 2ND WEEK (IU/L)| Dengue fever | 25 | 51.12 | 19.43 | 3.89 | 3.53 | <0.0001 |
|                | Chikungunya fever  | 27 | 37.41   | 5.26    | 1.01         |       |          |
| ALT ON 2ND WEEK (IU/L)| Dengue fever | 25 | 45.00 | 14.03 | 2.81 | 3.08 | <0.0001 |
|                | Chikungunya fever  | 27 | 35.96   | 5.81    | 1.12         |       |          |

Further when investigations were assessed in both groups, Platelet count were found to be significantly lower while Serum AST, ALT, AST at first and second follow up and ALT at first follow up were found to be significantly higher in dengue fever compared to Chikungunya fever.

While platelet counts were found to be significantly lower in DF (p=0.02), liver enzymes
were found to be consistently higher in DF at presentation (AST p= 0.001, ALT p=0.06) at 1 week (AST p= 0.002, ALT p=0.06) and at 2 weeks (AST p= 0.001, ALT p=0.003).

Clinical features and investigations in study subjects:

| Characteristics | DIAGNOSIS | Total | P value |
|-----------------|-----------|-------|---------|
| FEVER           |           |       |         |
| ABSENT          | Dengue fever | 1     | 10      |
| PRESENT         | Dengue fever | 24    | 42      | 0.012 |
| ECG             |           |       |         |
| BRADYCARDIA     | Dengue fever | 5     | 5       | 0.049 |
| LVH             | Dengue fever | 1     | 2       |
| NORMAL          | Dengue fever | 19    | 45      |       |
| RAISED          | Dengue fever | 0     | 7       | 0.006 |
| CRP             |           |       |         |
| NORMAL          | Dengue fever | 25    | 45      |
| RAISED          | Dengue fever | 2     | 17      | <0.001 |

Also fever, bradycardia were found to be significantly frequent in Dengue Fever, and Raised ESR and CRP were common in Chikungunya fever. Both ESR (p=0.006) and CRP (p<0.0001) showed increased frequency of raised levels in Chikungunya Fever. ECG showed significantly higher frequency of bradycardia in Dengue Fever.

Investigations in study subjects:

| DIAGNOSIS | N  | Mean | S.D. | Std. Error Mean | Std. Error | t  | P value |
|-----------|----|------|------|-----------------|-------------|----|---------|
| HB (gm%)  |    |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 13.19 | 1.88 | 0.38           | 2.38       | 0.53 |
| Chikungunya fever | 27.00 | 12.89 | 1.62 | 0.31           |             |
| TLC (/mm3) |    |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 5344.00 | 2430.72 | 486.14 | -1.71 | 0.09 |
| Chikungunya fever | 27.00 | 6803.00 | 3582.38 | 689.43 |         |
| T BIL (mg%) |    |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 0.69 | 0.25 | 0.05          | -1.44      | 0.16 |
| Chikungunya fever | 27.00 | 0.83 | 0.44 | 0.09          |             |
| ALBUMIN (gm%) |    |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 3.69 | 0.46 | 0.09          | -1.20      | 0.24 |
| Chikungunya fever | 27.00 | 3.92 | 0.83 | 0.16          |             |
| S. CREATININE (mg%) |     |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 0.78 | 0.15 | 0.03          |             |
| Chikungunya fever | 27.00 | 1.03 | 0.81 | 0.16          | -1.63      | 0.12 |
| RBS (mg%)  |    |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 103.20 | 12.52 | 2.50         | -1.74      | 0.09 |
| Chikungunya fever | 27.00 | 127.19 | 67.79 | 13.05 |         |
| ALT AFTER 1 WEEK (IU/L) |     |      |      |                 |             |    |         |
| Dengue fever | 25.00 | 84.16 | 76.79 | 15.36 | 1.93 | 0.06 |
| Chikungunya fever | 27.00 | 53.89 | 26.69 | 5.14          |             |

NO significant difference were observed in HB, TLC, T BIL, Albumin, S. Creatinine, RBS and ALT after 1 week
Investigations in study subjects:

| Characteristics | Dengue fever | Chikungunya fever | Total | P value |
|-----------------|--------------|--------------------|-------|---------|
| ECHO DECREASED  | 3            | 1                  | 4     | 0.341   |
| ECHO NORMAL     | 22           | 20                 | 42    |         |
| TAB Heptral GIVEN | 7         | 8                  | 15    |         |
| PT/INR NOT GIVEN | 18          | 19                 | 37    | 1.00    |
| BRADYCARDIA NG  | 20           | 25                 | 45    |         |
| BRADYCARDIA YES | 5            | 2                  | 7     | 0.184   |
| BRADYCARDIA NORMAL | 19      | 20                 | 49    |         |

Also frequency of findings in ECHO, PT/INR, bradycardia on clinical examination and intake of tab Heptral were found to be matched amongst the groups and found to be DF>CGF.

Diagnostic significance of various investigations in diagnosis of Dengue fever against Chickungunya fever in study subjects:

| Test Result             | Area   | Std. Error | P Value | 95% C.I. Lower | 95% C.I. Upper |
|-------------------------|--------|------------|---------|----------------|----------------|
| AST (IU/L)              | .836   | .058       | .000    | .722           | .950           |
| ALT (IU/L)              | .679   | .076       | .027    | .531           | .828           |
| AST AFTER 1 WEEK (IU/L) | .724   | .074       | .066    | .580           | .869           |
| ALT AFTER 1 WEEK (IU/L) | .636   | .079       | .092    | .482           | .790           |
| AST ON 2ND WEEK (IU/L)  | .786   | .062       | .000    | .665           | .907           |
| ALT ON 2ND WEEK (IU/L)  | .719   | .072       | .007    | .578           | .859           |

ROC curve was plotted for assessing diagnostic significance of various parameters to detect dengue fever amongst all subjects. AST showed maximum diagnostic significance with area under curve of 83.6% (p<0.0001).

Figure shows ROC curve analysis of various investigations. (Maximum for AST)
Beneficial effect of Tab Heptral in reducing liver enzymes in Dengue fever were also assessed by comparing change in liver enzymes in dengue subjects at first follow up and at second follow up. No significant difference was noted in Both liver enzymes at first follow up but significantly higher reduction in enzyme activity was found in both liver enzymes at second follow up in subjects who were given Tablet Heptral.

**DISCUSSION**

In Tropical countries like India where vector borne diseases like dengue and chikungunya are rampant, there is great necessity of early diagnosis and treatment to decrease mortality from dengue complications like dengue hemorrhagic fever and dengue shock syndrome.

Many a times there is diagnostic dilemma in differentiating dengue from chikungunya which are caused by same vector and in the same season (September to November in India). Also there is lack of diagnostic facilities in rural and tribal areas of India where costly investigations like dengue serology and chikungunya PCR are not available. In such situations serum transaminases which are available in all basic laboratories and are cheaper offer an diagnostic direction to differentiate dengue from chikungunya as dengue patients show more elevation of serum transaminases and early treatment can be initiated on that basis.

However even serum transaminases don’t show a upward trend in the first week of infection, its always better to consider each patient as dengue patient when diagnostic dilemma raises in order to avoid deadly complications of dengue.

In patients of dengue, basic blood tests like platelet count, packed cell volume, liver enzymes (ALT, AST) are done repeatedly on timely basis to guide the treatment and to know the prognosis. Also these are low cost tests and are available everywhere.

2D ECHO was done in our study in dengue patients with bradycardia or myocarditis as we have seen mortality in a single patient, but any literature for recommendation of routine 2D ECHO was not available for dengue patients.

We have used tab heptral (ademetionine) 400mg once or twice daily basis for dengue patients with severe transaminitis and its beneficial effect was found in the second week of follow up and many doctors contraindicate the routine use of heptral in dengue patients and the supporting evidence from literature is lacking.

| Beneficial effect of Tab Heptral | Tab Heptral | N | Mean | Std. Deviation | Std. Error Mean | t | P value |
|---------------------------------|------------|---|------|----------------|----------------|---|---------|
| Change in SGPT at first follow up | Not given | 18 | 2.11 | 38.04 | 8.97 | 1.96 | 0.06 |
| Given | 7 | -41.14 | 72.63 | 27.53 |
| Change in SGOT at first follow up | Not given | 18 | -63.83 | 131.75 | 31.05 | 1.60 | 0.23 |
| Given | 7 | -179.71 | 228.15 | 86.23 |
| Change in SGPT at second follow up | Not given | 18 | -27.22 | 50.97 | 12.01 | 2.92 | 0.05 |
| Given | 7 | -105.57 | 81.06 | 30.64 |
| Change in SGOT at second follow up | Not given | 18 | -83.67 | 150.18 | 35.40 | 2.79 | 0.01 |
| Given | 7 | -327.71 | 290.25 | 109.70 |
CONCLUSION

Recovery from chikungunya is previously considered universal and mortality due to the virus is rare and unusual and the prognostic value of liver transaminases is not significant.

Dengue fever and Chickungunya fever differ significantly in clinical and laboratory parameters. Liver enzymes specifically AST can promptly help to differentiate DF subjects from CF subjects. This finding should be interpreted keeping in mind the non significant difference of alcohol intake and Tablet. Heptral in two groups thus making the claim even stronger.

Further, Younger age, presence of high grade fever, bradycardia and normal ESR and CRP must raise suspicion of DF compared to CGF.

Tab. Heptral is beneficial in reducing liver enzymes in long term follow up though no literature for evidence was found.

BIBLIOGRAPHY

1. A STUDY ON SERUM ENZYME LEVELS IN VARIOUS LIVER DISEASES *Salma Mahaboob R1, Jayarami Reddy U2, John Basha S3,

2. Assessment of some biochemical tests in liver diseases By Prof. Mohamed Sharaf-Eldin Prof. of Hepatology & Gastroenterology Faculty of Medicine Tanta University, Egypt.

3. A fatal case of chikungunya virus infection with liver involvement. Chua HH , Abdul Rashid K, Law WC, Hamizah A, Chem YK, Khaıırul AH, Chua KB. Med J Malaysia. 2010 Mar;65(1):834.

4. Chikungunya fever in Singapore: Acute clinical and laboratory features, and factors associated with persistent arthralgia M.K. Win A. Chow F. Dimatatac C.J. Go Y.S. Leo ; Journal of Clinical Virology

5. Vector-Borne Diseases Section Division of Communicable and Environmental Diseases and Emergency Preparedness Tennessee Department of Health, Nashville, Tennessee ,2014

6. Centers for Disease Control and Prevention (http://www.cdc.gov/) chikungunya www.cdc.gov/chikungunya

7. Liver enzyme alteration: a guide for clinicians Edoardo G. Giannini, Roberto
Testa and Vincenzo Savarino From the Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy. CMAJ • February 1, 2005; 172 (3). doi:10.1503/cmaj.1040752.

8. PAHO WHO | Factsheet Chikungunya
9. WHO http://www.who.int/topics/dengue/e
10. https://www.cdc.gov/dengue/ Centers for Disease Control and Prevention
11. Wahid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health. 2000 Jun;31(2):25963.
12. Jayanta Samanta, Vishal Sharma, Department of Gastroenterology, Dengue and its effects on liver, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India World J Clin Cases. 2015 Feb 16; 3(2): 125–131. PMCID: PMC4317605
13. Wang XJ, Wei HX, Jiang SC, He C, Xu XJ, Peng HJ, Evaluation of aminotransferase abnormality in dengue patients: A meta analysis. Acta Trop. 2016 Apr;156:1306. Doi.10.1016/j.actatropica.2015.12.013. Epub 2015 Dec 29.
14. Kuo CH, Tai DI, Chang Chien CS, Lan CK, Chiou SS, Liaw YF., Liver biochemical tests and dengue fever. Am J Trop Med Hyg. 1992 Sep;47(3):26570.
15. Nguyen TL, Nguyen TH, Tieu NT. The impact of dengue haemorrhagic fever on liver function. Res Virol. 1997 Jul Aug; 148(4):2737.

ABBREVIATIONS
DF-dengue fever
DHF-dengue hemorrhagic fever
CGF-chikungunya fever
DSS-dengue shock syndrome
T BIL –total bilirubin
PT- prothrombin time
INR- international ratio

PCR –polymerase chain reaction