www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i7.26

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

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

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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	25.00	18.68	19.31	3.86	-4.88	0.00
	Chikungunya fever	27.00	44.07	18.24	3.51		
BMI (Kg/m^2)	Dengue fever	25.00	22.58	2.62	0.52	-12.39	0.02
	Chikungunya fever	27.00	21.07	1.93	0.37		

Characteristics		DIAGNOSIS		Total	P value
		Dengue fever	Chikungunya fever		
GENDER	Female	10	10	20	
	Male	15	17	32	1.00
DIET	NON VEG	12	11	23	
	VEG	13	16	29	0.780
TAB HEPTRAL	GIVEN	7	8	15	
	NOT GIVEN	18	19	37	1.00
ALCOHOL INTAKE	NO	25	24	49	
	YES	0	3	3	0.086

Table 1 indicated General characteristics of study subjects. This indicates that the dengue fever is significantly commoner in younger age group. Also two groups DF and CGF were matched for gender, diet habits, tab Heptral dosage and Alcohol intake.

[I would like to stress here on matching of group for alcohol intake as it has special reference to the conclusion of study...]

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 arthalgia 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	25.00	101120.00	104302.00	20860.43	-2.39	0.02
	Chikungunya fever	27.00	160670.00	74277.03	14294.62		
AST (IU/L)	Dengue fever	25.00	203.12	232.90	46.58	3.49	<0.0001
	Chikungunya fever	27.00	45.89	25.19	4.85		
ALT (IU/L)	Dengue fever	25.00	94.16	78.53	15.71		
	Chikungunya fever	27.00	48.15	28.87	5.56	2.76	0.01
AST AFTER 1 WEEK (IU/L)	Dengue fever	25.00	106.84	90.18	18.04	3.30	<0.0001
	Chikungunya fever	27.00	48.11	20.58	3.96		
AST ON 2ND WEEK (IU/L)	Dengue fever	25.00	51.12	19.43	3.89	3.53	<0.0001
	Chikungunya fever	27.00	37.41	5.26	1.01		
ALT ON 2ND WEEK (IU/L)	Dengue fever	25.00	45.00	14.03	2.81	3.08	<0.0001
	Chikungunya fever	27.00	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
		Dengue fever	Chikungunya fever		
FEVER	ABSENT	1	9	10	
	PRESENT	24	18	42	0.012
ECG	BRADYCARDIA	5	0	5	
	LVH	1	1	2	0.049
	NORMAL	19	26	45	
ESR (mm/Hr)	NORMAL	25	20	45	
	RAISED	0	7	7	0.006
CRP	NORMAL	23	12	35	
	RAISED	2	15	17	<0.0001

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	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		DIAGNOSIS		Total	P value
		Dengue fever	Chikungunya fever		
ECHO	DECREASED	3	1	4	
	NORMAL	22	26	48	0.341
TAB HEPTRAL	GIVEN	7	8	15	
	NOT GIVEN	18	19	37	1.00
PT/INR	Normal	23	27	50	
	Deranged	2	0	2	0.22
BRADYCARDIA	NO	20	25	45	
	YES	5	2	7	0.184
	NORMAL	19	26	45	

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 Variable(s)	Area	Std. Error[a]	P Value	95% C.I. Lower	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	**.006**	.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 ploted 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% ($p<0.0001$) .

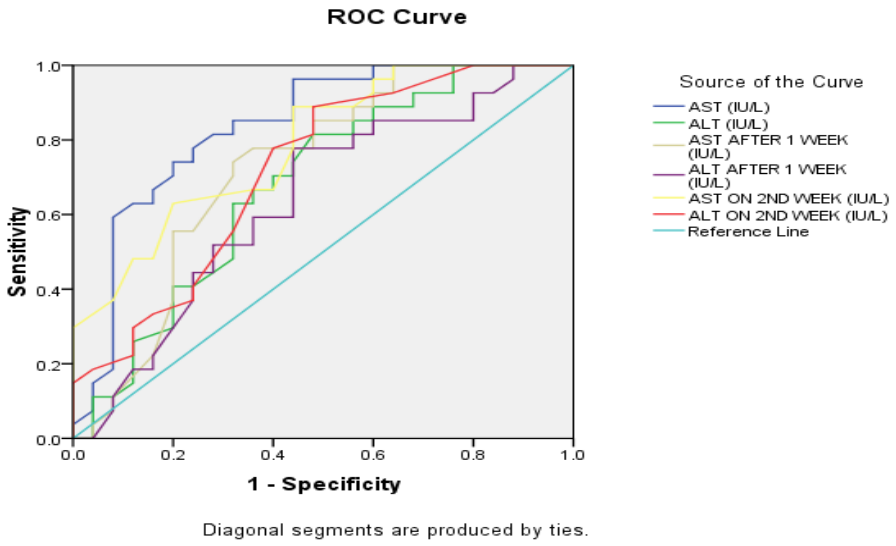

Figure shows ROC curve analysis of various investigations. (Maximum for AST)

Beneficial effect of Tab Heptral in reducing liver enzymes in Dengue fever

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	72.83	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		

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Beneficial effect of Tab Heptral in reducing liver enzymes in dengue fever were also assessed by compairing 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 ruraland 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.

Comparison of Chikungunya Virus Infection and Dengue Fever

Characteristic	Chikungunya virus infection	Dengue fever	Comments or additional information
Incubation Period	3-7 days (range 2-12 days)	4-7 days (range 3-14 days)	
Signs and symptoms	Fever, polyarthralgia (usually bilateral and symmetric and associated with distal joints such as the hands, feet, wrists, ankles, elbows and knees), headache, backache, myalgia pain, maculopapular rash, polyarthritis or conjunctivitis; rarely fatal	Fever, headache, retroorbital pain, arthralgia, myalgia and/or bone pain, rash and mild bleeding (e.g., nose or gums bleed, petechial rash, easy bruising); severe complications affecting circulatory system with dengue hemorrhagic fever	• Infections can be mild or asymptomatic • Co-infection is possible • Although each may have own characteristic symptoms, they cannot always be differentiated on signs/symptoms alone • Suspected chikungunya cases should be managed as dengue until dengue has been ruled out
Clinical lab findings	Mild thrombocytopenia (>100,000 /mm^3), lymphopenia, elevated liver enzymes (ALT, AST)	Thrombocytopenia (<100,000 /mm^3), lymphopenia, neutropenia and elevated liver enzymes (ALT, AST); more severe signs with dengue hemorrhagic fever	
Laboratory Testing			
Test type and sensitivity	• RT-PCR: most sensitive if collected ≤8 days of onset • Serology: IgM might not be positive until up to 4 days after onset; specimens collected <4 days after onset may be negative for IgM and testing should be repeated	• RT-PCR: most sensitive if collected ≤5 days of onset; • Serology: IgM might not be positive until up to 6 days after onset; specimens collected <6 days after onset may be negative for IgM and testing should be repeated	• Serum (collected in red-top or tiger-top tube) is preferred specimen for RT-PCR and serology • Positive IgG in absence of positive IgM is consistent with past infection • Serology: acute and convalescent serum (collected 10 to 14 days after symptoms onset) are recommended • Dengue negative cases (those that only test IgG positive for dengue) should also be investigated as potential chikungunya cases
Test availability	Focus Diagnostics (commercial lab) and CDC offer both RT-PCR and serology	Same commercial lab options. Additional labs can test for dengue but cannot simultaneously test for CHIK.	• Turnaround times vary by lab • Specimens tested at CDC should be coordinated through local health department. Priorities for CDC testing include: 1) those with compatible illness who traveled in group to area known to be endemic within past 14 days; or 2) those with compatible illness who traveled to area not known to be endemic within past 14 days (possible new transmission area); or 3) those with signs/symptoms who did not travel (possible local transmission); or 4) if commercial testing is not feasible

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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.

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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