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Original Article

Internal Medicine Section

Clinicobiochemical Difference of Patients Presenting with Dengue and Chikungunya during Post-Monsoon Season

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ABSTRACT

Introduction: India plays host to a number of vector-borne diseases, including dengue and chikungunya. Both diseases demonstrate a synchronised peak, and present with similar findings. An early accurate distinction between them is valuable for effective treatment and prevention of complications. Currently used diagnostic methods estimate either antibodies or antigens; the former are absent in the first week of disease, and testing for the latter is expensive.

Aim: To compare clinical profiles (history, examination) and laboratory parameters of patients with dengue fever and chikungunya fever.

Materials and Methods: Pre-diagnosed patients of dengue (50) and chikungunya (50) were studied to elicit patterns in clinical, haematological and biochemical profiles which may be used for differentiation. The time taken for resolution of symptoms, and complications, were studied prospectively. The data were analysed using Z-test.

Results: In both the diseases, patients present with short pyrexia (<1 week). The study found abdominal pain and bleeding significantly (p-value <0.001) more common in dengue than in chikungunya. It was discovered that joint pain and swelling was significantly (p-value <0.05) more common in chikungunya. Furthermore, leukopenia (<4000 WBCs/cumm) as well as moderate (50,000-100,000 platelets/microL) and severe (<50,000 platelets/microL) thrombocytopenia was significant for dengue. Milder (up to 3 times) SGOT and SGPT elevations were significant for chikungunya, whereas larger (>3 times) elevations were significant for dengue.

Conclusion: It may be concluded that the two diseases, despite their synchronised peak during post-monsoon season, and overlapping presenting symptoms, can be distinguished on the basis of clinical profiles of the patients, and a few basic laboratory tests. On studying a larger sample size, the presence of these associations could be determined with more certainty.

Keywords: Chikungunya fever, Dengue fever, Post-viral arthralgia/arthritis

INTRODUCTION

In the 21st century, as nations all over the world make bold strides in the eradication of vector-borne diseases, India still continues to bear a heavy burden of the cases. Epidemics of dengue and chikungunya occur frequently in the region, and take a huge toll on the infected people.

Dengue is a mosquito-borne viral infection [1]. There are four serotypes of Dengue Virus (DENV-1, DENV-2, DENV-3, and DENV-4), which produce similar clinical presentations [2], like headache, abdominal pain, vomiting, rash, and cutaneous hypersensitivity. Haemorrhagic manifestations are present in a few. There are two types of dengue recognised by the WHO-dengue fever; and severe dengue fever [3].

Chikungunya is another mosquito-borne viral disease. It is caused by the transmission of an alpha-virus called Chikungunya Virus (CHIKV) [4]. In Chikungunya, patients usually present with sudden-onset high-grade fever, severe arthralgia, myalgia, and skin rash [5]. It is usually benign, but sometimes may cause severe neurological illness [6].

Both viruses are spread by the *Aedes aegypti* mosquito, which is well-adapted to the urban environment [4,7]. It commonly breeds in artificial containers filled with water, leading to a sharp rise in its population during monsoon [8].

A recent WHO estimate indicates approximately 50-100 million cases of dengue per year worldwide [9]. Similarly, since 2005, countries in the South-East Asian Region of WHO alone have reported over 1.9 million cases of chikungunya [10].

Currently, both the diseases are diagnosed using serological tests. For dengue, diagnostic tests available detect either NS1 antigen of the DENV, or the IgM antibodies produced in the body as a result of the infection [11]. NS1 antigen is detectable in serum till 4-5 days after infection. Around the 5th day, IgM antibodies appear in blood [11,12].

Similarly, for the diagnosis of Chikungunya, serological methods are used to detect either the presence of RNA CHIKV through Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR), or IgM antibodies produced by its interaction with the host's immune system, which appear in the blood after one week of illness has elapsed. RT-PCR has highest reactivity during the first 4-5 days [10].

RT-PCR and NS1 antigen tests, although highly sensitive, are expensive tests, which diminishes their acceptability. On the other hand, performing ELISA to detect IgM antibodies delays the diagnosis of the two diseases. Moreover, 83.3% of the Indian population lives in rural areas [13], and may not have an access to such complex diagnostic procedures.

Therefore, an attempt was made to distinguish between the two diseases by elucidating patterns in the clinical, haematological, radiological and biochemical profiles, which may be considered diagnostic. This can save crucial time in beginning the prompt treatment of the patients. Eliminating the need for serological testing would prevent an unnecessary economic burden on the infected patients. Also, it would ensure that even workers in peripheral health centers can diagnose and differentiate the two diseases, and adequately prevent complications. Therefore, this study aims to compare clinical profiles (history, examination) and laboratory

parameters of the patients with dengue fever and chikungunya fever, focusing especially on the patterns of arthritis and arthralgia experienced by them.

MATERIALS AND METHODS

This was a cross-sectional study of patients presenting to medicine Outpatient Department (OPD) and Emergency Department in Hakeem Abdul Hameed Centenary (HAHC) Hospital, Jamia Hamdard situated in South Delhi, India. After obtaining permission from the Institutional Ethics Committee of Hamdard Institute of Medical Sciences and Research (HIMSR) to conduct the study, patients who satisfied the inclusion criteria and those who gave written informed consent were selected, and the study was conducted in the months of May 2016 to July 2016.

Inclusion and Exclusion Criteria

All consenting patients above the age of 16 years who had been diagnosed with dengue or chikungunya using antigen testing or serological testing were included. Patients with obvious signs of localised infections, such as, ear discharge; dysuria; purulent discharge from wound; etc., and patients with mixed infections were excluded from the study.

The study was conducted on 100 patients (50 chikungunya + 50 dengue) who had been pre-diagnosed using serological tests.

Detailed histories of the patients were noted and thorough clinical examinations were performed. All the complications (especially those relating to joints) were recorded. Apart from joint pain and swelling, the patterns of joint involvement including, number of joints involved-oligoarthritis (up to 4) or polyarthritis (>4); grade of pain; and duration of pain; were also recorded.

The pain grading was done using a self-designed scale which characterised pain into four grades:

- Grade 0: No pain
- Grade 1: Mild pain, but able to perform all activities
- Grade 2: Moderate pain; not able to perform all usual activities
- Grade 3: Severe pain; not able to perform basic daily activities
- Grade 4: Severe pain, and bedridden

Duration of pain was noted during follow up of patients and was graded as <1 month, 1-3 months, 3-6 months and >6 months.

Laboratory parameters that were recorded included complete haemogram, as well as Liver Function Tests (LFT's) which consists of Total Serum Bilirubin (SBT), liver enzymes (SGOT, SGPT), Alkaline Phosphatase (ALP), and serum albumin.

Patients' platelet count and LFT was recorded daily. For this study, lowest value of platelet count and the highest values of SGOT and SGPT of each patient have been included. SGOT/SGPT was also graded as mild elevation (<3 times of lab upper limit of normal) and severe elevation (>3 times). Similarly, platelet count was graded as mild (100,000-150,000 platelets/μL), moderate (50,000-100,000/μL) and severe (<50,000 platelets/μL) thrombocytopenia.

All patients underwent Ultrasound (USG) abdomen and chest X-ray to look for ascites, organomegaly or pleural effusion.

STATISTICAL ANALYSIS

All the data were collected and tabulated in excel sheets. These data were analysed statistically using Z-test method to obtain p-values. A p-values of less than 0.05 have been considered statistically significant to establish a correlation between certain findings and either dengue or chikungunya fever.

RESULTS

In this study, pre-diagnosed patients of dengue (50) and chikungunya (50) were taken [Table/Fig-1].

It was found that abdominal pain and bleeding were highly significant (p<0.001) for dengue over chikungunya [Table/Fig-2].

Patient demographics		Chikungunya	Dengue
Total patients		50	50
Mean age and SD		37.8±12.2 years	24.86±10.2 years
Sex	Males	20 (40%)	29 (58%)
	Females	30 (60%)	21 (42%)

[Table/Fig-1]: Demographic details of the patients.

Clinical parameters	Chikungunya	Dengue	p-value with significance value
Fever duration	6.32 days	4.74 days	
Abdominal pain present	13 (26%)	31 (62%)	0.00068 (p<.001)
Vomiting present	23 (46%)	38 (76%)	0.42161 (p>0.05)
Itching present	18 (36%)	25 (50%)	0.16371 (p>0.05)
Rash present	20 (40%)	20 (40%)	1.0000 (p>0.05)
Bleeding present	6 (12%)	18 (36%)	0.00710 (p<0.05)

[Table/Fig-2]: Clinical history of the patients.

Both dengue and chikungunya were analysed on the basis of joint condition. Higher percentage of patients in chikungunya presented with joint pain. Along with the pain, swelling was present in more chikungunya patients as compared to dengue patients [Table/Fig-3]. Both these results were statistically significant.

Joint parameters			Chikungunya (n=50)	Dengue (n=50)	p-value
Joint pain and swelling	Joint swelling present		26 (52%)	3 (6%)	0.00136 (p<0.05)
	Joint pain present		45 (90%)	22 (44%)	0.0001 (p<0.0010)
	Duration of pain	<1 month	15	11	0.18635 (p>0.05)
		1-3 months	8	8	0.09078 (p>0.05)
		3-6 months	10	2	0.19754 (p>0.05)
		>6 months	12	1	0.03581 (p>0.05)
	No. of joints	4 or less	24	16	0.12439 (p>0.05)
		>4 joints	21	6	0.14275 (p>0.05)
	Grade of pain	1	9	13	0.0026 (p<0.05)
		2	8	1	0.14097 (p>0.05)
		3	12	7	0.66947 (p>0.05)
		4	16	1	0.00843 (p<0.05)

[Table/Fig-3]: Patient joint condition.

On evaluation of laboratory tests, leukopenia (<4000 WBCs/cumm) was present in a significantly higher percentage of patients of dengue (46%) than chikungunya (26%). Moderate and severe thrombocytopenia were both statistically significant for dengue more than chikungunya [Table/Fig-4].

Furthermore, mild (up to 3 times) elevations of SGOT and SGPT were significantly associated with chikungunya. However, larger elevations (more than 3 times) in SGOT and SGPT levels were found statistically significant for dengue. Alkaline phosphatase elevation was more common in the dengue patient group, and this was statistically significant [Table/Fig-4].

Radiological investigations were used to assess pleural effusion, ascites, hepatomegaly, and splenomegaly, as shown in [Table/Fig-5]. All four criteria's were more common in dengue than in chikungunya. However, while all others were significant for dengue, hepatomegaly wasn't significant for either disease [Table/Fig-5].

Laboratory parameters		Chikungunya	Dengue	p-value
Anemia (<12 gm/dL)		22 (44%)	17 (34%)	0.31034 (p>0.05)
Leukopenia (<4000 cell/cumm)		13 (26%)	23 (46%)	0.04246 (p<0.05)
Thrombocytopenia	100,000-150,000/µL	9 (18%)	3 (6%)	0.07088 (p>0.05)
	50,000-100,000 µL	12 (24%)	22 (44%)	0.03990 (p<0.05)
	<50,000 µL	4 (8%)	23 (46%)	0.00009 (p<0.05)
Elevated SGOT	Up to 3 times	27 (54%)	9 (18%)	0.00047 (p<0.05)
	>3 times	7 (14%)	37 (74%)	0.00000 (p<0.05)
Elevated SGPT	Up to 3 times	34 (68%)	14 (28%)	0.00021 (p<0.05)
	>3 times	2 (4%)	24 (48%)	0.00001 (p<0.05)
Elevated alkaline phosphatase		4 (8%)	13 (26%)	0.02044 (p<0.05)

[Table/Fig-4]: Laboratory values of the patients.

Radiology parameters	Chikungunya	Dengue	p-value
Pleural Effusion	6 (12%)	15 (30%)	0.03183 (p<0.05)
Ascites	3 (6%)	20 (40%)	0.00019 (p<0.05)
Hepatomegaly	6 (12%)	10 (20%)	0.28057 (p>0.05)
Splenomegaly	1 (2%)	10 (20%)	0.00594 (p<0.05)

[Table/Fig-5]: Radiological findings of the patients.

DISCUSSION

Tropical infections like dengue and chikungunya have contributed significantly to healthcare burden of India. Both diseases commonly cause epidemics during (or soon after) the monsoon season [14] and have largely similar clinical presentations, which complicates their diagnosis.

In this study, 50 laboratory diagnosed patients each of dengue and chikungunya were evaluated and compared on the basis of history, clinical examination, haematology, biochemistry and radiology.

Mean age of patients in dengue (24.86 years; range: 16-60 years) was lower than mean age of patients in chikungunya (37.8 years; range: 17-81 years). Male to female ratio was higher for dengue (1.38; males-58%, females-42%) than for chikungunya (0.66; males- 40%, females- 60%). These findings were in concurrence with other studies, like Tomashek KM et al., that generated similar data claiming dengue commonly presented in younger (mean-15.4 years) males (53%), as compared to chikungunya (mean age- 24.3 years; males-47.1%) [15]. Moreover, since dengue and chikungunya are immune-mediated diseases as the immune system of younger patients is stronger so the percentage of infected individuals developing disease manifestations is higher.

Average duration of fever for dengue was 4.74 days and that for chikungunya was 6.32 days, thus establishing dengue and chikungunya as possible aetiologies of short pyrexia (less than 1 week). Tomashek KM et al., have claimed an extremely large percentage of patients of both diseases present within five days of onset (dengue-91.9%; chikungunya-97.8%) [15].

Severe abdominal pain in dengue is considered a marker for severe dengue [16], however mild pain may be seen in uncomplicated dengue fever as well, according to Shaikh N et al., [6], Tomashek KM et al., Sahadeo N et al., (55.8%; 31.2%) [15,17]. It is found less commonly in patients of chikungunya (31.6%; 6.7%) [15,17]. The present study also found abdominal pain to be highly significant (p-value<0.001) for patients with dengue (62%) as compared to patients with chikungunya (26%). In addition, vomiting was found more often in dengue (76%) than in chikungunya (46%), but this finding was not statistically significant (p-value >0.05), which was unexpected as vomiting is often considered a typical sign of dengue, as claimed by many studies, including Mallhi TH et al., Itching was found in 50% dengue patients and 36% chikungunya patients, and its development was usually seen at the time of recovery [18]. Rash is a common sign of chikungunya as well as dengue [9,10], and in the present study both patient groups presented it equally (40%). Bleeding in acute febrile illness is an important complication of dengue [9], and in this study, it was observed to be highly significant (p-value <0.001) for dengue (36%) as compared to chikungunya (12%).

An analysis of joint condition showed that, although dengue is renowned as “break bone fever” [19]; joint pain is associated much less frequently with dengue (44%) when compared with chikungunya (90%) (p-value <0.01). This mimicked the findings of Tomashek KM et al., Sahadeo N et al., (Dengue-57.8%, Chikungunya-81% [15]; Dengue-60%, Chikungunya-83.3% [17]). The present study was the first to assess both diseases on the basis of grade of pain (graded from 1-4), number of joints involved (1-4; or more than 4 joints), and duration it lasted (up to 1 month; 1-3 months; 3-6 months; or more than 6 months). It was found that while lower grade pain (Grade 1) was significant for dengue (59.09%; chikungunya-20%); higher grade pain (Grade 4) was significantly associated with chikungunya (61.53%; dengue-4.54%) (p-value <0.05). Larger proportion of patients with joint pain in dengue (50%) tended to heal within a month than in chikungunya (33.33%), whereas joint pain lasting more than 6 months was discovered to be significant for chikungunya (26.66%) over dengue (4.54%). In addition, swelling of the joints was noticed significantly (p-value <0.05) more often in chikungunya (52%) than in dengue (6%), which can be compared favorably with the results of Tomashek KM et al., (chikungunya-43.4%; dengue-12% [15]).

Complete Blood Counts (CBCs) and Liver Function Tests (LFT) were studied for both patient groups. Anaemia (<12 gm/dL of Hb), although noted in both dengue (34%) and chikungunya (44%), had no significant association with either, and was likely the result of inclusion of known anaemic patients into the study caused by widespread nutritional deficiencies present in Indian population [20]. Leukopenia (<4,000/cumm, WBCs), in resemblance with the results of Tomashek KM et al., (dengue-73.8%; chikungunya-21% [15]), was significantly associated with dengue (46%) as compared to chikungunya (26%). This could be due to the bone marrow suppression that occurs in both diseases.

In our study, 96% dengue patients and 50% chikungunya patients presented with thrombocytopenia (platelet count <150,000/µL). Tomashek KM et al., Paniz-Mandolfi AE et al., have also established similar ratios [15,21]. The present study additionally sought a comparison on the basis of degree of thrombocytopenia. Mild thrombocytopenia (100,000-150,000/µL) was seen more commonly in chikungunya (18%) than dengue (6%). Both moderate (50-100,000/µL) and severe (<50,000/µL) thrombocytopenia was significant (p-value <0.05, and <0.001 respectively) for dengue (44%, and 46% respectively) over chikungunya (24%, and 8% respectively).

Fernando S et al., established that dengue is associated with progressive liver injury that tends to peak around the end of first week of disease, resulting in a concurrent rise in serum SGOT and SGPT levels [22]. Similarly, chikungunya too has been linked (albeit less frequently) with raised liver enzymes [23]. In the present study, mild SGOT and SGPT elevations (up to 3 times) were noted in 54% and 68% chikungunya patients respectively, and 18% and 28% dengue patients respectively. This difference was statistically significant (p-value<0.05). However, severe SGOT and SGPT elevations (more than 3 times) were present in 74% and 48% dengue patients respectively, and 14% and 4% chikungunya patients respectively, which too was statistically significant (p-value<0.05). Raised alkaline phosphatase levels (>147 IU/L) were also present significantly more often in dengue (26%) than in chikungunya (8%).

Prior to the present study, Paniz-Mondolfi AE et al., reported hepatomegaly as common in chikungunya, and absent in dengue [21]. This was in contrast with this study which linked hepatomegaly more often with dengue (20%) instead of chikungunya (12%), although not significantly. Furthermore, pleural effusion, ascites, and splenomegaly were also perceived to be present in a statistically significantly higher proportion of subjects belonging to the dengue patient group (30%, 40%, and 20% respectively) as compared to those of the chikungunya patient group (12%, 6% and 2% respectively). All four parameters have been noted as atypical manifestations of dengue by Mia MW et al., (hepatomegaly- 54%; pleural effusion- 42%; ascites- 41%; splenomegaly-18% [24]). No similar study of imaging findings in case of chikungunya could be found.

The aforementioned findings can be utilised extensively to yield a more rapid and cheaper system of diagnosis of the two diseases, permitting an earlier initiation of treatment, which can be potentially life-saving. A simpler diagnostic method based on these clinical and laboratory parameters would permit healthcare workers in peripheral centers to diagnose patients. This could be beneficial for the patient both in terms of convenience as well as cost effectiveness, as expensive serological testing could be avoided.

Although, multiple studies have compared dengue and chikungunya, a detailed basis of distinction between the two has not yet been documented. The findings noted by this study could prove beneficial to physicians in primary healthcare centers to make accurate diagnosis.

LIMITATION

However, a large multi centric comparative analysis is required to confirm this. The present study recruited a small sample of patients (50) each of both the diseases, and a larger sample size would lend more credibility to the data generated. It is recommended that special emphasis be placed on LFT parameters as most of these were found to have statistically significant associations with one of the two diseases.

CONCLUSION

In conclusion, although, dengue and chikungunya have similar clinical presentations, it is possible to differentiate between them on the basis of clinical features (abdominal pain, bleeding) LFT (SGOT, SGPT, Alkaline Phosphatase), CBC (Leukopenia, thrombocytopenia) and radiological findings (splenomegaly, ascites, and pleural effusion).

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