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An Emerging Threat of Dengue and Chikungunya Co-infection: Need of Developing a Pre-diagnostic Screening Tool

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SS, AR and AW did the study design and the literature search. Authors SS, VS and AY prepared the manuscript and were involved in the critical analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

Dengue and Chikungunya infections have caused large outbreaks globally and millions of people have been affected worldwide. They are transmitted by *Aedes aegypti* and *Aedes albopictus* and can cause potentially severe acute illnesses and or debilitating chronic disease. Coinfection with both diseases is not new and has been reported on patients from Asian, African and Pacific countries. The need to differentiate between two infections is also very important because minute differences in treatment and, misdiagnosis can hamper epidemiological understanding of both diseases.

Use of symptoms differentiation, scoring systems and simple laboratory parameters is discussed in this article which can be used to accurately identify cases of mono and co-infections. The paper emphasizes on development of a pre-screening diagnostic criteria to differentiate between these two diseases which will not only reduce unnecessary testing but will also prevent misdiagnosis.

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1. INTRODUCTION

Limited resources and the great diversity of acute febrile illness (AFI) etiologies in tropical regions challenge diagnosis, treatment, and public health responses to endemic and epidemic diseases [1]. Widely distributed in tropical and subtropical areas throughout the world, Chikungunya virus (CHIKV) and Dengue virus (DENV) cause acute illnesses mainly characterized by fever and arthralgia. CHIKV has recently caused large outbreaks, and DENV is a global plague, with tens of millions of cases each year [2,3]. Dengue fever is caused by a class of pathogens called as *Flavivirus* that belongs to the family of Flaviviridae and Chikungunya, being caused by the *Alphavirus* of family *Togaviridae* [4].

Both dengue and chikungunya diseases are transmitted by *Aedes aegypti* and *Aedes albopictus* and can cause potentially severe and or debilitating chronic disease. While dengue has been recorded as the most rapidly spreading mosquito-borne viral disease in the world, chikungunya has recently re-emerged after an interval of several decades. It represents a risk for millions of people in the Indian Ocean areas, Africa, Southeast Asia and more recently has spread to the Caribbean, Pacific and Europe [5].

Dengue is endemic in both urban and semi urban areas of India and was first isolated in India in 1945. Delhi situated in the northern part of India, had outbreaks of dengue due to different dengue virus types in 1967, 1970, 1982, 1988, 1996 and 2003 [6] In India, the chikungunya virus was first isolated in 1963 in Kolkata followed by epidemics in Chennai, Pondicherry and Vellore in 1964; in Visakhapatnam, Rajahmundry and Kakinada in Andhra Pradesh in 1965 and in Nagpur, also in 1965. The last officially recorded outbreak in India was reported in Barsi in Maharashtra in 1973. The disease re-emerged in India in October 2005 after remaining silent for nearly 32 years. Andhra Pradesh was the first state to report this disease in December 2005. Kerala was the worst affected state in 2007 with approx. 3.6 million fever cases. Thereafter it has been repeatedly reported from 13 different states of India and has resulted in 1.4−6.5 million estimated cases across the country [7]. The capital of India, New Delhi is still battling with increased number of Dengue and Chikungunya cases in post monsoon season of 2016.

2. COINFECTION – A REALITY

Coinfection with DENV and CHIKV has been reported on patients from Asian, African and Pacific countries [5]. These two diseases now co-circulate in many countries and pose a challenge to clinicians because they may require different clinical management even though their manifestations can be similar [8].

Both dengue and chikungunya viruses often co-circulate in the mosquito and are transmitted to human beings as co-infections following the mosquito bite [9]. Many factors influence the geographical spread of both viruses, including vector distribution (both are spread by Aedes mosquitoes), human travel, urbanization, and climatic changes [8]. Kushwah RBS et al. [10] in their study from India confirmed the fact of co-habitation of dengue and chikungunya viruses in field mosquitoes. It reported the concurrent infection of DENV serotypes and CHIKV from the same pool of Ae. Aegypti collected from field sites.

Nimmannitya et al. [11] in 1962 reported the first case of coinfection in Thailand. Human coinfection with DENV and CHIKV have been reported in India since 1967 [12].

Subsequent serologic investigations in Southern India indicated that the 2 viruses can coexist in the same host [13]. The rates of coinfection in various areas in India have been different. The prevalence of co-infection using serological methods have been reported as 2.7% by Kalawat et al. [14], 2.8% by Omarjee et al. [15], 12.4% by Taraphdar et al. [16] and 6.7% in londhey et al. [9].

Several studies have been done to describe the severity of dengue-chikungunya coinfection.

Two studies, Chahar et al. [13] and Gandhi et al. [17] have described increased severity with coinfection. The mortality rate in Gandhi et al was 12% in coinfected patients as compared to 2% in monoinfected patients [17]. Various other studies did not report any increase in mortality with coinfection [15,16]. This makes the situation unclear and warrants further investigations.

3. IS DIFFERENTIATION NECESSARY?

The need to differentiate between two infections is also very important because of minute

differences in treatment and, misdiagnosis can also hamper epidemiological understanding of both diseases. Misdiagnosis of dengue fever as chikungunya (or missing a dengue infection when coinciding with chikungunya) risks delaying or disrupting dengue-specific intensive supportive treatment which can have a ten-fold impact on likelihood of progression from dengue fever to severe disease. It also risks inappropriate prescription of arthralgia-alleviating nonsteroidal anti-inflammatory drugs (often employed in treating chikungunya patients) which could lead to severe bleeding in patients with thrombocytopenia or Dengue Hemorrhagic Fever (DHF). The opposite and potentially more likely scenario in which chikungunya infection is misdiagnosed as dengue (or missed in a co-infected individual) masks the true geographical extent of CHIKV and population at risk of infection [18]. In some patients chikungunya can progress to cause chronic arthritis. Hence these patients have to be followed up on a long term basis [9]. 5.6% of the patients developed chronic arthritis over a period of 2 years after an acute chikungunya infection [19].

Since DENV and CHIKV share a seasonal transmission cycle and have a number of similarities in clinical presentation, they are difficult to distinguish without specialized serologic or molecular diagnosis. We in this article are going to discuss various modalities which might be able to differentiate between the two diseases using clinical features, and simple laboratory measures which have been devised in various articles.

4. DISEASE DIFFERENTIATION

The disease can be diagnosed simply by performing serological and molecular diagnostic methods but the application of both tests on every patient is not cost efficient especially in a low resource setting. We have studied various articles on differentiation of the diseases on basis of scoring system, symptom differentiation and simple laboratory variables and will combine them in this article.

4.1 VAS Scoring

VAS is a unidimensional measure of pain intensity [20]. It is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme. The pain VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. Using a ruler, the score is determined by measuring the distance on the 10-cm line. A higher score indicates greater pain intensity [21].

In londhey et al. [9], among the mono and dual infections, all mono CHIKV and 90% dual infections showed severe VAS score of 6-10, while in case of mono DENV, only 55% of patients showed severe VAS score. Some part of this finding was reproduced in Galate et al(2016) where all CHIKV infected patients had VAS score between 6-10 and only 15.78% of dual infected patients had VAS score less than 6. This particular finding can be used to differentiate dengue mono infection from dual infection and chikungunya mono infection.

There was an important finding highlighted by Galate et al. [22], which can further differentiate between CHIKV mono infection and dual infection as both have severe VAS score. The combination of Severe VAS and restriction of joint movement is more common in CHIKV mono infection than Dual infection. All the 6 patients with CHIK mono-infection had VAS score of 6–10 with restricted joint movement as compared to only 1 patient with dual infection which was statistically highly significant [9,22].

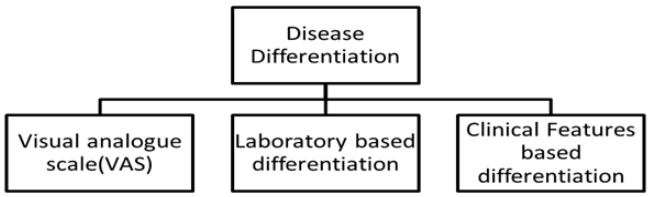

Fig. 1. Various factors that can be used to differentiate between the Dengue and Chikungunya infection before using the molecular and serological diagnostic tests

4.2 Clinical Features and Laboratory Values Mediated Differentiation

1. Wonderful decision trees using clinical variable and laboratory variable are present. The decision trees use predictors of chikungunya and dengue to assist doctors in both well-resourced and resource-limited settings in diagnostic decision making. The decision trees are available in the article written by Lee et al. [8].

2. Various clinical features can be used to define the illness and differentiate between them. The following Fig. 4 demonstrates various features which can be used to differentiate:

   To summarize, there are some features that can be combined and therefore can lead to formation of a clinical diagnostic criteria to decide the inclusion or exclusion of a disease.

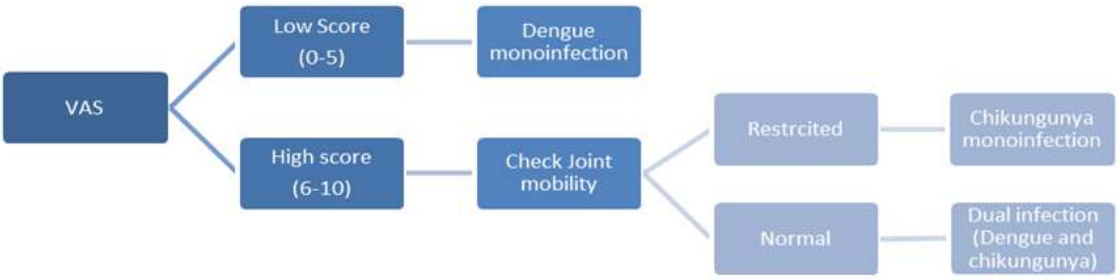

Fig. 2. Flowchart to differentiate between Mono infection (Dengue/Chikungunya) and dual infection

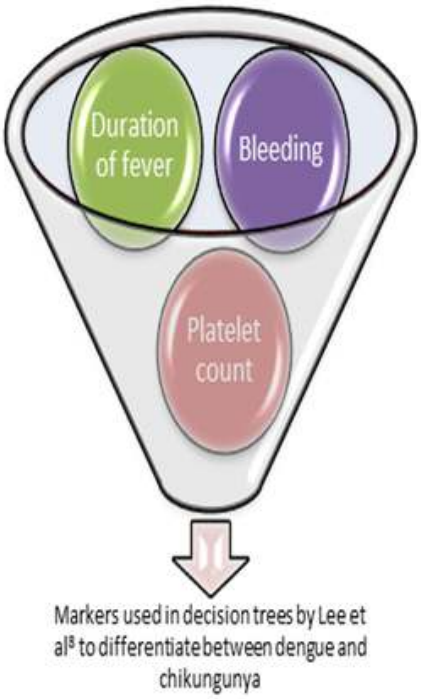

Fig. 3. Various markers used by Lee et al. [8] in making decision trees to differentiate between dengue and chikungunya in a well-resourced setting and a resource-limited setting

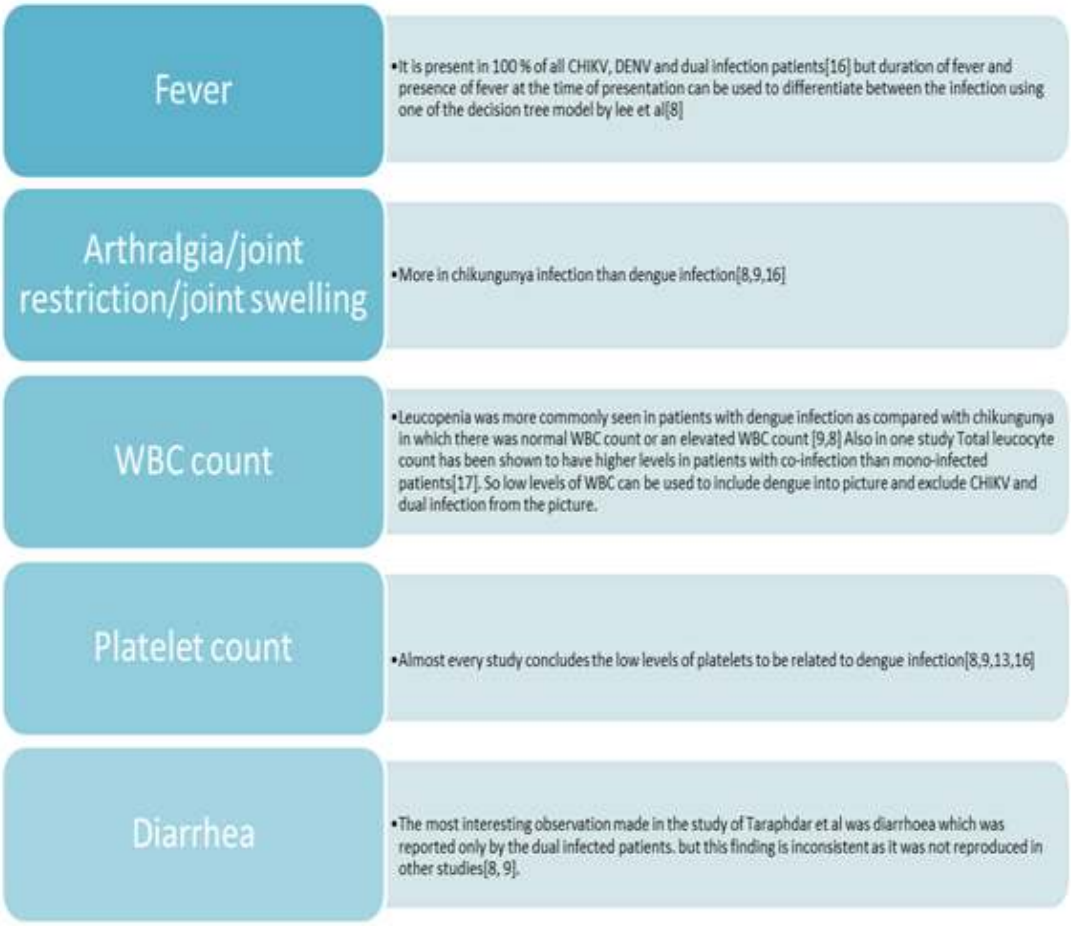

Fig. 4. Demonstration of clinical features that can be used to differentiate between Dengue and Chikungunya infection

5. CONCLUSION

In this article evidence has been provided from various articles about the prevalence of dual infection in patients suffering from acute febrile illnesses. The reemergence of chikungunya has increased the dilemma in the diagnosis of acute febrile illness. We, thus suggest formation of protocols using clinical and low cost laboratory measures to correctly diagnose the illness so that proper laboratory and molecular diagnostic measures can be used in each patient in a cost effective manner. The Government of various states has capped the price of Dengue and Chikungunya tests at Rs. 600 each [23]. Formulating the Pre-Screening criteria will reduce the cost of an additional test in every patient.

We suggest the use of following table to devise a clinical screening tool:

S. no	Variable under study	Dengue	Chikungunya
1.	VAS Score	Low score (0-5)	High score (6-10)
2.	Joint mobility	Normal	Restricted
3.	Platelet count	Low	Normal
4.	Bleeding	Present	Absent
5.	WBC count	Low	High/normal
6.	Fever/Illness	>2 days or illness > 3 days	<2 days or Illness <3 days

Higher the score in either of the subsection will increase the probability of having that particular disease. Equal scores may suggest co-infection. Our next target should be to use this table of differentiation and prove the statistical significance of such a tool to differentiate between these two infections.

This is the appropriate time to formulate a study based on the variables described to assess the accuracy of such a screening tool. The validity of such a tool need to be studied on different population groups of various ages which will allow calculating the sensitivity and specificity of these variables as a whole.

Also there is a need to study the entomological and epidemiological aspects of dengue and chikungunya causing mosquitoes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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