

CLINICAL FEATURES OF ACUTE FEBRILE THROMBOCYTOPAENIA AMONG PATIENTS ATTENDING PRIMARY CARE CLINICS

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ABSTRACT

Introduction: Identifying clinical features that differentiate acute febrile thrombocytopenia from acute febrile illness without thrombocytopenia can help primary care physician to decide whether to order a full blood count (FBC). This is important because thrombocytopenia in viral fever may signify more serious underlying aetiology like dengue infection.

Objective: The aim of this study was to compare the clinical features of acute febrile patients with thrombocytopenia and acute febrile patients without thrombocytopenia.

Methodology: This was a clinic-based cross-sectional study from May to November 2003. Consecutive patients presenting with undifferentiated fever of less than two weeks were selected from the Primary Care Centre of Hospital Universiti Kebangsaan Malaysia and Batu 9 Cheras Health Clinic. Clinical features of these patients were recorded and FBC examination was done for all patients. Thrombocytopenia was defined as platelet count $<150 \times 10^9/L$. The odds ratio of thrombocytopenia for each presenting symptoms was calculated.

Result: Seventy-three patients participated in this study. Among them, 45.2% had thrombocytopenia. Myalgia and headache were common among all patients. However, nausea and vomiting occurred significantly more often among patients with thrombocytopenia than in patients with normal platelet count (OR 2.2, 95% CI 1.1-4.5).

Conclusion: Acute non-specific febrile patients presenting with symptoms of nausea and vomiting may have higher risk of thrombocytopenia and should be seriously considered for FBC.

Key words: viral infection, dengue, clinical features, thrombocytopenia.

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INTRODUCTION

Dengue infection is the most common arthropod-borne infection in the tropics where it carries significant morbidity, mortality and immense economic burden to the countries affected.¹ The incidence of dengue infection is on the rise in Malaysia.² Early diagnosis of dengue infection is important in order to minimise mortality.³ Diagnosis of dengue infection is supported if there is thrombocytopenia, the presence of which often signify more serious type of dengue infection.⁴⁻⁶ All these point to the importance of detecting thrombocytopenia in suspected dengue patients.

It is difficult to differentiate dengue infection from other viral infections due to the overlap in the symptoms.⁷⁻¹² To make the distinction, one may decide to order full blood count (FBC) for all febrile patients. This practice is often impractical due to the large number of febrile patients in the

outpatient clinic. Thus, clinical features that suggest the presence of thrombocytopenia help primary care physician to decide whether full blood count is necessary. The objective of this study is to identify clinical features that differentiate between febrile patients with and without thrombocytopenia.

METHODS

This was a cross-sectional study conducted at two primary care clinics (Primary Care Centre of Hospital Universiti Kebangsaan Malaysia and Batu 9 Cheras Health Clinic) from May 2003 to November 2003. Consecutive febrile patients who fulfilled study criteria were invited to participate in the study. The inclusion criteria were age ≥ 12 years with a history of fever for less than 2 weeks. Fever was defined as oral temperature $>37.5^\circ C$. Patients were excluded if localised source of infection can be identified, e.g. urinary tract infection. Illnesses with pathognomonic clinical features e.g. varicella infection, measles, rubella, scarlet fever and dengue haemorrhagic fever. Consents were taken from all eligible patients before enrolment. Their clinical features were recorded using standard data collection sheet and FBC examination was done for all patients. The investigators were blinded to the FBC result until all clinical features were recorded. In this study, patients with thrombocytopenia (defined as platelet count $<150 \times 10^9/L$) were managed as dengue infection until the

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availability of their dengue IgG and IgM status.¹³ Patients with normal platelet count were called back on day 5 of illness for a repeat clinical assessment and FBC examination in order not to miss any dengue infection.

The data collection sheet also asked for demographic data of patient, days of fever, presenting symptoms (headache, myalgia, nausea and vomiting, arthralgia, retro-orbital pain and rash) and FBC results.

We analysed the data using SPSS version 11. For non-categorical and normally distributed data, Student's t-test was used. For categorical data, χ^2 tests were used and odds ratios were calculated accordingly for each of the presenting symptom. Significant level of difference was defined as $p < 0.05$. Calculated minimal sample size of 61 patients (using Epi-Info 2000) was required for in this study based on the estimated prevalence of dengue infection of 20% (95% confidence interval; worst estimated of 10%) among patients presented with acute non-specific febrile illness.

We obtained ethical approval from the Research and Ethics Committee of Medical Research Center UKM.

RESULTS

One hundred fifty-three patients were screened, 49 did not give consent for the study and 17 were excluded for not fulfilling the criteria. Fourteen patients defaulted follow up as they claimed to be well and refused reassessment. Therefore, only 73 patients were included in the study. Among them, 33 patients (45.2%) had thrombocytopenia. Mean age of the patients in this study was 27.3 years (range 12-65, $SD \pm 11.1$). The majority of the patients were male (67.6%) and 73% were Malays, followed by Chinese (12.2%) and Indians (9.5%). There was no significant gender and ethnicity difference between patients with thrombocytopenia and patients with normal platelet count (Table 1).

Table 1: Baseline characteristics of patients with and without thrombocytopenia

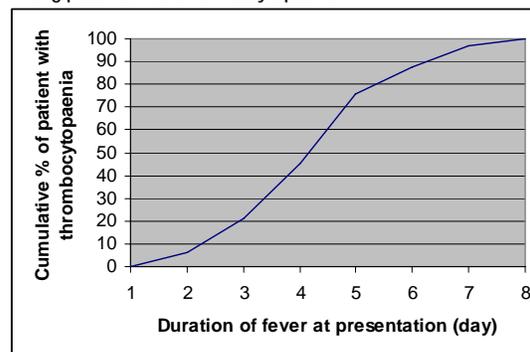
| Demographic characteristics | Platelet count | |
|-----------------------------|----------------|------------------|
| | Normal | Thrombocytopenia |
| Mean age, years | 29.1 | 25.1 |
| <i>Sex</i> | | |
| Male | 29 (72.5) | 20 (60.6) |
| Female | 11 (27.5) | 13 (39.4) |
| <i>Ethnicity</i> | | |
| Malay | 31 (77.5) | 22 (66.7) |
| Non-Malay | 9 (22.5) | 11 (33.3) |

All comparisons statistically not significant ($p > 0.05$)

Patients presented to the clinic at different days of fever. These ranged from 2-10 days of fever (mean days of fever 4.7 ± 1.7). Patients with thrombocytopenia had a mean duration of fever at presentation of 4.7 (\pm S.D 1.5) days; while those with normal platelet count had a mean duration of 4.0 (\pm S.D 1.9) days. Most patients (94%) with thrombocytopenia presented on or at least by day 3 of

fever (Figure 1). If duration of fever ≥ 3 days at presentation was taken as a variable to determine the odds of having thrombocytopenia against patients with normal platelet count, the OR was 5.9 (95% CI 1.2-28.8) which was statistically significant.

Figure 1. Cumulative rate of thrombocytopenia by duration of fever among patients with thrombocytopenia



Common symptoms reported among patients with thrombocytopenia were myalgia (69.7%), headache (66.7%), nausea/vomiting (69.7%) and arthralgia (39.4%). When the clinical features presented by the 2 groups were compared, only nausea/vomiting were significantly different (OR 2.81; 95% CI 1.1-7.4); other clinical features did not show any significant difference (Table 2).

Table 2: Comparison of the presenting symptoms among patients with and without thrombocytopenia

| Symptom | Platelet count | | OR ^a (95% CI) |
|--------------------------------------|----------------|------------------|--------------------------|
| | Normal | Thrombocytopenia | |
| Presented at or after day 3 of fever | 26 (65%) | 31 (93.9%) | 5.88 (1.20-28.8)* |
| Myalgia | 32 (80) | 23 (69.7) | 0.58 (0.20-1.68) |
| Headache | 25 (64.1) | 22 (66.7) | 1.20 (0.46-3.16) |
| Nausea/vomiting | 18 (46.2) | 23 (69.7) | 2.81 (1.07-7.41)# |
| Arthralgia | 26 (40) | 13 (39.4) | 0.98 (0.38-2.50) |
| Retro-orbital pain | 9 (23.1) | 6 (18.2) | 0.77 (0.24-2.43) |
| Rash | 5 (12.5) | 8 (24.2) | 2.24 (0.66-7.67) |

^aOdds ratio (95% confidence interval), * $p = 0.04$, # $p = 0.03$

DISCUSSION

Generally the symptoms of patients with thrombocytopenia and patients with normal platelet count were similar except for nausea and vomiting. Nausea and vomiting was found to be significantly different between these two groups of patients. The odds of thrombocytopenia among patients with complaints of nausea and vomiting were about twice. Could it be postulated that the pathological response resulting in thrombocytopenia may also give rise to the symptoms of nausea and vomiting? Whatever the explanation might be, the importance of detecting thrombocytopenia cannot be over emphasised. Hence we should consider a FBC test among patients presenting with symptoms of nausea and vomiting as the odds of developing thrombocytopenia is

high and they might be at risk of severe disease which require admission.

Another important aspect to look at is the association of duration of fever and the presence of thrombocytopenia. Although there was no difference in the mean duration of fever among patients with thrombocytopenia and normal platelet count, there were 5 times the odds of thrombocytopenia if patients presented at day 3 of fever compared to those presented on day 1 or 2 of fever. This is not unexpected, as dengue patients usually develop thrombocytopenia at day five to seven of illness when the fever starts to subside.^{5,14} The mechanism for such occurrence is due to increases peripheral platelet destruction and marrow suppression.¹⁴ Hence, it is advisable that all patients presenting on day 3 of fever should be offered a FBC test. On the other hand, doing a full blood count in a patients presenting early (i.e. day 1 or 2 of illness) may not be appropriate as the rate of picking up a thrombocytopenia is low.

In this study, the data was collected prospectively in order to standardise the data collection and to minimise incomplete data. All selected patients selected had acute non-specific febrile illness from the outpatient setting. This was an important feature of this study as the studies in the past mainly recruited patients from hospital or suspected cases of dengue from outpatient setting, who might not represent the typical patients with acute non-specific febrile illness. Furthermore, previous studies had not looked into the association of clinical features and thrombocytopenia among patients presented with acute non-specific febrile illness. Presence of thrombocytopenia helps clinicians in assessing the severity of the illness;⁴⁻⁶ therefore it is critical for health care professionals to be able to detect thrombocytopenia among patients with acute non-specific febrile illness. Misdiagnosing a case of dengue infection without thrombocytopenia may not be as disastrous as misdiagnosing a case of dengue infection with thrombocytopenia, because dengue infection with normal platelet count represents a milder form of DF and do not require admission.

CONCLUSION

Patients with symptoms of nausea and vomiting had higher risk of having thrombocytopenia. The majority of thrombocytopenic patients presented on day 3 of fever or later. Hence requesting a full blood count on all patients with undifferentiated fever for more than two days should be recommended in order to detect thrombocytopenia. In primary care centre without FBC testing facility, febrile

patients with nausea and vomiting should be referred for FBC in view of the higher possibility of thrombocytopenia. This is important because clinical diagnosis of dengue infection is unreliable. Adopting this approach in managing patients with non-specific acute febrile illness can guide health care professionals to be more selective in requesting a full blood count.

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COMMENTARY

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Das Gupta E. Commentary on "Clinical features of acute thrombocytopenia among patients attending primary care clinics." *Malaysian Family Physician*. 2006;1(1):18

Studies that evaluate the utility of clinical history and physical examination was popularised by the *JAMA*'s Rational Clinical Examination series.¹ In this series, few authors hail from primary care and relatively few cited papers were conducted in the primary care setting. This is somewhat disturbing. Primary care doctors rely almost entirely on the selective use of history and physical examination to make diagnosis. But, the utility of these clinical skills that are used daily in the diagnostic tasks are inadequately evaluated in the setting where they are used.

It is thus of interest to read this paper by Tong *et al* who attempted to evaluate the predictive value of history in the detection of thrombocytopenia among febrile patients.² The gist of their findings is this: patients with acute febrile illness of unapparent cause in primary care may be having thrombocytopenia if the fever is of longer duration (≥ 3 days) or is associated with nausea/vomiting. Although the authors did not verify the aetiology of fever in their patients, it is likely that there were more dengue patients in the thrombocytopenic group - this is consistent with the longer duration of fever at presentation. What about the association between thrombocytopenia and nausea/vomiting? Chadwick *et al*³ did not find a higher prevalence of nausea or vomiting when comparing the serologically proven dengue and non-dengue patients in hospitalised patients. On the other hand, Seet *et al*⁴ found that nausea and diarrhoea (but not vomiting) were significantly more common among Chinese immigrant workers who contracted dengue (compared to historical controls).

Even if the gastrointestinal symptoms noted in this study were causally related to dengue infection, I am doubtful if nausea/vomiting per se is useful as a diagnostic aid in clinical practice. This is because both symptoms are rather ill-defined and can occur in a wide variety of febrile illnesses, many of which are not even primarily gastrointestinal diseases or clinically serious. In fact, in a diagnostic study searching for the predictors of streptococcal tonsillitis, Kreher *et al*⁵ found that nausea and vomiting are somewhat more common in streptococcal than non-streptococcal tonsillitis. In our search for clinical predictors, we need to bear in mind that a red herring may be found instead. Another point to note: in diagnostic study it is useful to report the performance of the diagnostic test

(e.g. sensitivity, predictive values, etc).⁶ In spite of the statistical significance obtained, the test item evaluated may not achieve a respectable level in terms of the test performance.

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