

Prevalence of Non-Dengue Thrombocytopaenia among Adult Patients Presenting with Acute Febrile Illness in Primary Outpatient Clinics

Tong SF, Aziz NA, Chin GL

Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur.

ABSTRAK

Sebahagian dari pesakit yang mengalami demam akut dengan trombositopenia, tidak semestinya mengidap penyakit denggi. Merawat mereka seperti mana mereka mengidap denggi adalah tidak wajar. Prevalens penyakit tersebut masih tidak diketahui. Objektif kajian ini adalah untuk menentukan prevalens penyakit demam akut dengan trombositopenia yang bukan denggi di kalangan pesakit demam akut tidak spesifik dari klinik pesakit luar. Ini adalah satu kajian keratan rentas di klinik. Semua pesakit yang mengadu demam kurang dari dua minggu yang tidak spesifik dari Pusat Perubatan Primer Hospital Universiti Kebangsaan Malaysia (HUKM) dan Klinik kesihatan Batu 9 Hulu Langat dipilih untuk mengambil bahagian. Kajian kiraan darah lengkap (full blood count) pada hari pertama mereka ke klinik dan serologi denggi pada hari ke 5 selepas demam bermula dijalankan. Seramai 73 pesakit berjaya mengambil bahagian dari Mei hingga November 2003. Di antara mereka, 47.9% (35) pesakit didapati mempunyai trombositopenia. Seramai 40% (14) dari mereka yang mempunyai trombositopenia adalah negatif dalam ujian serologi denggi. Maka, prevalens penyakit demam akut dengan trombositopenia yang bukan denggi adalah 19.2%. Dengan ketaranya, sebahagian pesakit di kalangan pesakit demam akut tidak spesifik, menunjukkan ujian serologi denggi negatif. Pesakit-pesakit ini harus dibezakan dari kalangan pesakit demam akut tidak spesifik, kerana mereka mungkin berbeza dari segi riwayat penyakit dan rawatannya.

Kata kunci: pesakit luar, penyakit demam akut, demam virus, trombositopenia, denggi.

ABSTRACT

A proportion of patients with acute viral fever with thrombocytopaenia does not necessary have dengue infection. Managing them indiscriminately as dengue infection may not be appropriate. The prevalence of this problem is not exactly known. The objective of this study is to determine the prevalence of acute non-dengue febrile thrombocytopaenia among adult patients presenting with acute non-specific febrile illness in an outpatient setting. This was a clinic-based cross sectional study. Consecutive patients presenting with non-specific febrile illness of less than two weeks were selected from the Primary Care Centre of Hospital Universiti Kebangsaan Malaysia (HUKM) and the Batu 9 Cheras Health Clinic. Full blood count was done on the day of visit and dengue serology was done on day five of illness for all patients enrolled. Seventy three patients participated in this study from May to November 2003. Among the patients, 35 (47.9%) were noted to have

Address for correspondence and reprint requests: *Dr. Tong Seng Fah, Department of Family Medicine, Faculty of Medicine, National University of Malaysia (UKM), Jalan Yaacob Latif, Cheras, 56000 Kuala Lumpur, Malaysia. E-mail: tsf@mail.hukm.ukm.my*

thrombocytopenia. Fourteen (40%) patients with thrombocytopenia were serologically negative. The prevalence of non-dengue febrile thrombocytopenia was 19.2%. A significant number of patients with acute non-specific febrile illness with thrombocytopenia were negative for dengue serology. These patients should be differentiated from those with acute febrile thrombocytopenia, as they might differ in their natural history from those with dengue infection, and hence require different management strategies.

Keywords: outpatient, acute febrile illness, viral fever, thrombocytopenia, dengue.

INTRODUCTION

Non-specific viral febrile illness is a common encounter in an outpatient clinic (Teng et al. 2003). It is an important entity especially in countries where dengue infection is prevalent. This is because one of the common presenting symptoms of dengue infection is non-specific febrile illness (Gibbons and Vaughn 2002). Many clinicians would report and manage a case of acute non-specific viral febrile illness with thrombocytopenia as dengue infection based on clinical assessment alone (Audit of Dengue notification in Pusat Perubatan Primer HUKM 2004).

However, dengue infection is only one of the many causes of acute febrile thrombocytopenia. Other causes of febrile thrombocytopenia include scrub typhus, chikungunya fever, infectious mononucleosis, malaria, typhoid fever, leptospirosis and acute human immunodeficiency virus conversion disease (Vaughn and Green. 2000). Reporting every case of acute non-specific viral febrile thrombocytopenia as dengue infection would lead to over reporting. Furthermore, managing all cases of acute non-specific viral febrile illness with thrombocytopenia as dengue infection may not be appropriate as acute non-dengue viral febrile illness with thrombocytopenia may differ in their natural history and treatment from dengue infection. Some require less intensive monitoring as in chikungunya fever; some may need antibiotics such as scrub typhus

and typhoid fever; some may have other serious outcome such as splenic rupture in infectious mononucleosis and acute human immunodeficiency virus conversion disease. Hence it is important to differentiate patients presenting to the outpatient setting with acute non-dengue febrile thrombocytopenia from those having dengue infection. Deparis et al in 1998 reported 15.5% of acute non-dengue febrile patients have thrombocytopenia. There is no published data on the prevalence of such an entity among patients presenting with acute non-specific viral febrile illness. Knowing its prevalence will help us estimate the magnitude of the problem. The objective of this study was to determine the prevalence of non-dengue febrile thrombocytopenia among febrile patients presenting to the outpatient clinic.

MATERIALS AND METHOD

This was a cross sectional study of a group of patients attending the Primary Care Center of Hospital Universiti Kebangsaan Malaysia (HUKM) and Batu 9 Health Clinic Hulu Langat, from May to November 2003. Consecutive patients who fulfilled the study criteria were invited to participate in the study. The inclusion criteria were age 12 years and above with a history of fever of less than two weeks. Fever was defined as recorded oral temperature of more than 37.5°C. Patients were excluded if there was an apparent localised source of infection e.g. urinary tract infection or acute abdomen. Any illness with pathognomonic

clinical features e.g. varicella infection, measles, rubella, scarlet fever and obvious features of dengue haemorrhagic manifestations were also excluded. Consents were taken from all eligible patients before enrolling them into the study.

Full blood count examination was carried out for every patient seen. Patients were assumed to have dengue infection if thrombocytopenia (platelet count of $\leq 150 \times 10^9/L$) was detected. They were managed as per protocol for management of dengue infection. All the other patients with normal platelet count were called back on day 5 of illness for a repeat full blood count so as not to miss any possibility of thrombocytopenia. Dengue serology was done for all patients on day five of illness, as early blood sampling of less than day five of illness might yield false negative results. If the patients require admission anytime during the study, the data was then collected from hospital records.

Dengue serology tests were run with PanBio Rapid Immunochromatography method in the virology laboratory, HUKM. The methods, reagents used and interpretation of results were as described by the manufacturer. Primary acute dengue infection is defined as a positive serology test of IgM alone. Secondary infection is defined as a positive IgG with or without a positive IgM. Collectively, both primary and secondary infections constitute acute dengue infection. A negative result is when both IgG and IgM are negative.

Statistical analysis and sample size calculation

Analysis of the data was carried out using SPSS version 11. The denominator is the total number of cases presented as non-specific febrile illness. Calculated minimal sample size of 61 patients was required, based on the estimated prevalence of non-dengue thrombocytopenia of 20% (95% confidence interval; worst estimated of 10%) among patients presenting with acute

non-specific viral febrile illness. Ethics approval was obtained from the research and ethics committee of the Medical Research Center UKM.

RESULTS

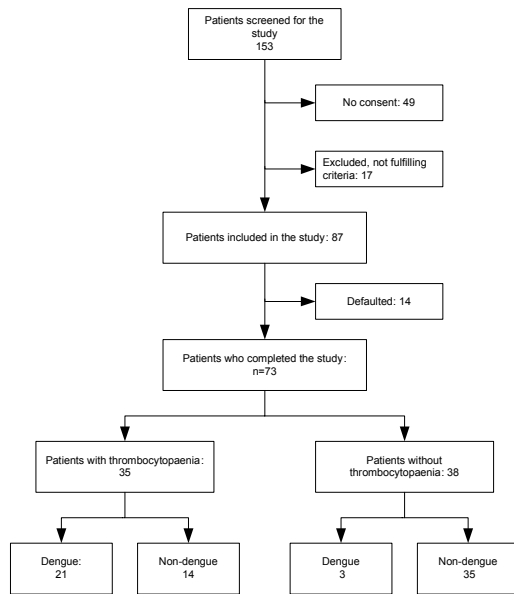
153 patients were screened, 49 did not give consent for the study and 17 were excluded for not fulfilling the criteria. Fourteen patients defaulted follow up as they claimed to be well and refused reassessment. Complete data was available for 73 patients. Mean age of the patients in this study was 27.3 years (27.3, $SD \pm 11.1$). Their baseline characteristics are presented in table 1. Figure 1 summarises the number of patients enrolled in this study. The majority of the patients enrolled were Malay (72.6%).

Table 1: Baseline characteristics among patients presenting with non-specific febrile illness.

Demographic characteristic		n=73
Mean age (\pm SD) in years		29.1(\pm 12.9)
Sex	Male	49
	Female	24
Race	Malay	53
	Chinese	9
	Indian	7
	Others	4

Thirty five of 73 patients were found to have thrombocytopenia. Hence, the prevalence of thrombocytopenia among acute non-specific febrile illness was 47.9%. Among these patients, 40% (14) were serologically negative for dengue infection, and only 60% (21) were diagnosed to have dengue infection. The overall prevalence of acute non-dengue viral thrombocytopenia among patients presenting with non-specific viral fever is therefore 19.2%.

Figure 1: Patients enrolled in the study.



Of the remaining 38 patients with the normal platelet count, three were tested positive for dengue serology. Therefore, total number of dengue infection was 24 and hence the prevalence of dengue infection among patients presenting with non-specific viral fever was 32.9%.

DISCUSSION

This study confirmed that thrombocytopenia is common among adult patients with non-specific febrile illness. About half of them (47.9%) had thrombocytopenia. A significant proportion of patients with thrombocytopenia (40%) were serologically negative for dengue infection. Hence, equating all patients with thrombocytopenia as having dengue infection may lead to over diagnosis. However, one has to be cautious when interpreting this data. Panbio Rapid Immunochromatography test kit was used as a gold standard for diagnosis in this study. Serologically negative result for dengue does not rule out dengue infection. Antigen detection by polymerase chain reaction, viral culture or paired serology

should be used as the gold standard for diagnosis (WHO 1997). Therefore, even though Panbio Rapid Immunochromatography test kit has very good sensitivity and specificity, false positive and negative test results do occur. In reference to a local study by Lam et al., the false negative rate of this Panbio Rapid test was 0% (sensitivity of 100%) and the false positive rate was 11% (specificity of 89%) (Lam and Devine 1998). Whereas, Vaughn et al. demonstrated that 80% of dengue patients would show a diagnostic level of secondary dengue infection by day 1 of defervescence using haemagglutination-inhibition test (HAI, in detecting IgG) which gave a false negative of 20%. Day of defervescence was defined as the day when the temperature dropped below 38°C which commonly occurs around day 5 to 7 of illness (Vaughn et al. 1997). In the present study, the false negative rate for serological diagnosis using Panbio Rapid Immunochromatography test was probably less than 20%. Considering the rate of false negative as 20%, there would still be 11 patients (33.3%) with seronegative results and the prevalence of acute non-dengue viral thrombocytopenia among patients presenting with non-specific viral fever would therefore be 15.1%.

Deparis et al reported that 15.5% of acute non-dengue febrile patients have thrombocytopenia (Deparis et al. 1998). However, patients from this study were among those suspected to have dengue infection, and not all patients with acute non-specific febrile illness were from an outpatient setting. From this data, it is evident that non-dengue thrombocytopenia is a significant entity that should be differentiated with dengue infection. It is important to differentiate between these two groups, as acute non-dengue febrile thrombocytopenia might be different in their natural history from those with dengue infection. At present, all patients with acute non-specific febrile illness and thrombocytopenia are assumed to have dengue fever, and they are managed as such. This

may not be the appropriate management as the other causes of febrile thrombocytopenia require different management strategies.

In this study, data were collected prospectively in order to standardise data collection and to minimise incomplete data. The patients selected were all from outpatient clinic with non-specific viral febrile illness and the result confirmed that dengue infection indeed is a common problem among them during the non-epidemic season, whereby the prevalence was 32.9%. The prevalence of dengue infection is consistent with that of other studies, where dengue infection is endemic, ranging from 21%-35% (Trofa et al. 1997, Deparis et al. 1998, Akram et al. 1998, Kalayanarooj et al. 1998). However, 32.8% of the patients eligible for this study were unwilling to participate. They were probably suffering from a milder form of non-dengue viral fever. Hence, the true prevalence might be lower than 32.9%. During an epidemic episode, the prevalence might increase up to as high as 90% (Teerakut et al. 1990). There is no published data on the prevalence of dengue infection among patients presenting with undifferentiated fever from Malaysia. Chin et al. in 1993 reported 69.4% and 85.7% of clinically diagnosed dengue fever and dengue haemorrhagic fever respectively were serologically positive. However, these were among patients with clinically diagnosed dengue infection and not all patients with undifferentiated fever (Chin et al. 1993).

CONCLUSION

Non-dengue febrile thrombocytopenia is a significant entity among adult patients with acute non-specific febrile illness. 19.5% of these patients had non-dengue febrile thrombocytopenia and 40% of thrombocytopenic febrile patients were seronegative for dengue infection. It may not be appropriate to manage them as dengue infection because the course of the

illness may differ significantly from dengue infection. A future study on this group of patients is needed in order to gain better understanding of its aetiological agents, natural history and hence guide us on the appropriate management.

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