EVIDENCE OF INFLUENZA OR INFLUENZA-LIKE-ILLNESS PRECEDING ACUTE CORONARY SYNDROME

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Abstract. This observational study determined the prevalence of influenza and influenza-like-illness (ILI) in patients hospitalized for acute coronary syndrome (ACS). Serological confirmation and a clinical history of influenza or a recent acute upper respiratory infection were obtained in 376 patients admitted to Maharaj Nakhon Chiang Mai Hospital, Thailand, from June 2006 through May 2007 for ACS. We found evidence of confirmed influenza preceding ACS in 47 patients (12.5%) and for recent ILI in 41 patients (11%). There were more influenza and ILI patients admitted in the winter than in other months. Influenza vaccination may be protective in high risk patients.

INTRODUCTION

Influenza can exacerbate underlying medical conditions such as cardiovascular disease, and the course of infection may become complicated by viral or secondary bacterial pneumonia (Advisory Committee on Immunization Practice, 2006). Many studies have shown the incidence of pneumonia is common as an influenza complication (Harper *et al,* 2002). Acute coronary syndrome (ACS) can be triggered by influenza infection (Madjid *et al,* 2003). The mechanism by which influenza might trigger ACS is not well understood, but systemic infections can cause inflammatory responses that may influence the development and progression of vascular injury. Influenza infection has been suggested as an explanation for winter peaks of acute myocardial infarction (AMI) (Sheth *et al,* 1999). An observational study showed that the annual incidence of cardiovascular mortality has a significant correlation with influenza pneumonia mortality, with peaks that lagged behind influenza infection by about 2 weeks (Glezen *et al,* 1982). Some clinical studies have concluded that myocardial infarction is preceded by upper respiratory tract infection (Pesonen and Sittonen 1981; Meier *et al,* 1998; Zheng *et al*, 1998). In a study conducted among nearly 35,000 individuals, influenza epidemics were associated with a peak in autopsy confirmed deaths from acute myocardial infarction and ischemic heart disease (Madjid, 2007b).

Influenza vaccination is associated with a significantly reduced risk of cardiovascular events for individuals with coronary artery disease, cerebrovascular disease and in elderly people (Vu *et al,* 2002; Nichol *et al,* 2003, 2007). The American Heart Association/American College of Cardiology (AHA/ACC) recommends influenza vaccination as part of comprehensive secondary prevention in adults with coronary and atherosclerotic vascular disease (Davis *et al,* 2006). In Thailand, the estimated incidence of influenza in 2006 from the Ministry

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of Public Health was 11.45 per 100,000 persons (Ministry of Public Health, 2007). There is no official recommendation for influenza vaccination in the elderly or for individuals with cardiovascular disease in Thailand, and influenza vaccine is administered to less than 1% of the population annually (Simmerman *et al,* 2004). Recognition of influenza as a trigger for ACS would provide a strong rationale for recommending influenza vaccination in people with coronary heart disease. In this study, we looked for evidence of recent influenza infection prior to acute coronary syndrome among patients admitted to a tertiary care hospital in northern Thailand.

MATERIALS AND METHODS

Patients

Between June 2006 and May 2007, eligible ACS patients admitted to Maharaj Nakhon Chiang Mai Hospital who survived at least 14 days after admission and gave informed consent were studied for evidence of recent influenza infection by taking a history of recent upper respiratory tract infection (fever, runny nose, sore throat, myalgia, headache, productive cough) prior to ACS admission, and by conducting serologic tests for influenza A and B antibodies. The study was approved by the Ethical Review Committee of Faculty of Medicine, Chiang Mai University, Thailand.

Clinical and laboratory evaluation

ST segment elevation acute myocardial infarction (STEMI) was diagnosed in patients presenting with chest pain longer than 20 minutes duration, post-cardiac arrest, shock, syncope, or cardiac dyspnea with new ST-segment elevation at the J point (greater than or equal to 0.2 mV in V1, V2, or V3 or greater than or equal to 0.1 mV in other leads) in 2 or more contiguous leads or with the presence of a new left bundle branch block in the setting of positive cardiac markers (MB isoenzyme of creatinine kinase >2 fold above the upper normal limit, or troponin-T or troponin-I >0.1 ng/ml). Patients were diagnosed to have non-ST-segment elevation myocardial infarction (NSTEMI) if presenting with chest pain longer than 20 minutes, post-cardiac arrest, shock, syncope, or cardiogenic dyspnea with ST depression or T-wave inversion with the presence of at least one positive biochemical marker for myocardial necrosis. Unstable angina was diagnosed in those presenting with chest pain, abnormal electrocardiographic findings suggesting cardiac ischemia, and absence of positive biomarkers (Srimahachota *et al,* 1998).

Basic demographic data were collected from all eligible patients. A history of recent upper respiratory tract infection was evaluated, and paired sera (2 weeks apart; admission day and day 14 after admission) were tested for influenza A and B infection by enzyme-linked immunosorbent assay (ELISA) (Euroimmun AG, Luebeck, Germany) at the viral laboratory of the Maharaj Nakhon Chiang Mai Hospital.

Patients were evaluated and classified into one of four categories regarding influenza: *ie*, recent influenza, recent influenza-like illness, possible influenza and no evidence of recent influenza. Recent influenza was diagnosed if patients had a definite serological test *ie* two-fold increase in IgG titer or IgM:IgG ratio ≥ 1.1 regardless of clinical symptoms. Those with a serum IgM:IgG ratio ≥ 0.8 to<1.1, or less than a 2-fold increase in IgG titer, were classified as having possible serological evidence of influenza infection. Negative serology was diagnosed if the serum IgM:IgG ratio was < 0.8 or a rising IgG titer was absent. Patients having a definite URI history, *ie* a history of fever and at least one of the following symptoms, runny nose, sore throat, myalgia, headache, productive cough, with negative or possible serology were diagnosed as having a recent influenza-like illness. The diagnosis of possible

recent influenza was made if patients had a possible URI history, and/or possible serologic results. Patients without the above clinical diagnoses and laboratory results were diagnosed as without evidence of recent influenza.

RESULTS

Between June 2006 and May 2007, 428 ACS patients were hospitalized at Maharaj Nakhon Chiang Mai Hospital. In this group, there were 376 eligible patients. The 52 ineligible patients were excluded because of loss to follow-up or death within 14 days of admission. One hundred ninety-eight patients (53%) were men. The average age was 64.7±10.7 years. One hundred eighty-four patients (48.9%) had ST elevation myocardial infarction. Non-ST elevation myocardial infarction and unstable angina were diagnosed in 132 (35.1%) and 60 patients (16%), respectively (Table 1).

Among the recruited 376 patients, 47 (12.5%) met our diagnostic criteria for recent influenza; 34 (9%) by serology alone and 13 (3.5%) by serology and possible or definite symptoms (Table 2). Forty-one patients (11%) had recent influenza-like illness. Possible recent influenza was diagnosed in 50 patients (13%); 26 (7%) by possible URI history, 20 (5%) by possible serology results and 4 (1%) by both possible URI history and serology. There were 238 patients (63%) with neither clinical nor serological evidence of recent influenza (Table 2). There were 74 patients with a possible or definite serological test. Of these, 45 (60.8%) had evidence of influenza A and 4 (5.4%) had evidence of influenza B. Finally, 25 patients (33.8%) had serological evidence for both influenza A and B. The frequencies of influenza diagnosis by month and season are shown in Figs 1 and 2. There were significantly higher numbers influenza and influenza-like illness among admitted ACS patients in the

Table 1
Patient baseline characteristics.

Parameter	
Average age (yrs)	64.7±10.7
Sex (M:F)	1.1:1
Diagnosis, *N* (%)	
STEMI	184 (48.9%)
NSTEMI/UA	187 (61.1%)
Underlying disease/risk factors, *N* (%)	
Diabetes	156 (41.5%)
Hypertension	250 (66.5%)
Smoking	126 (33.5%)
Dyslipidemia	295 (78.5%)
Family history of coronary artery disease	37 (9.8%)

Table 2
The frequency of each influenza diagnosis according to predefined diagnostic criteria.

	History of URI		
	Negative	Possible	Definite
Serology			
Negative	238 (63.3%)[a]	26 (6.9%)[b]	38 (10.1%)[c]
Possible	20 (5.4%)[b]	4 (1%)[b]	3 (0.8%)[c]
Definite[d]	34 (9%)[d]	3 (0.8%)[d]	10 (2.7%)[d]

[a]Without recent influenza	238 (63.3%)
[b]Possible recent influenza	50 (13.3%)
[c]Recent influenza-like illness	41 (10.9%)
[d]Definite recent influenza	47 (12.5%)

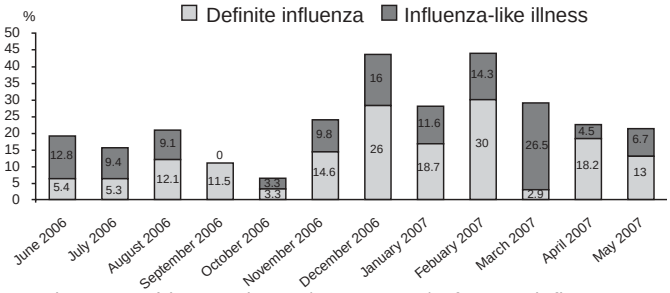

Fig 1–Monthly prevalence (percentage) of recent influenza and influenza-liked illness in patient with acute coronary syndrome.

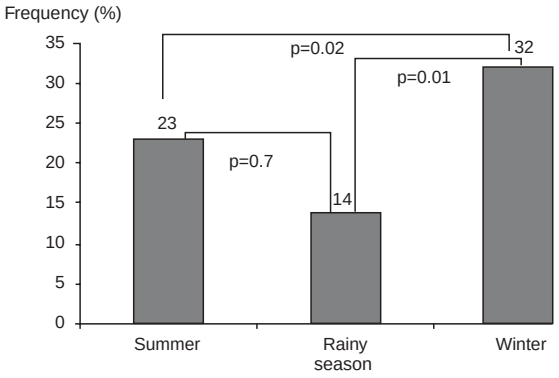

Fig 2–Seasonal prevalence of recent influenza and influenza-like illness showing a significantly higher prevalence in winter.

winter. The highest rate was for both influenza and influenza-like illness was 44% in February 2007.

DISCUSSION

This observational study, focused on the prevalence of recent influenza and influenza-like illness among patients admitted with ACS to a tertiary care hospital. We found evidence of confirmed influenza preceding ACS in 47 patients (12.5%) and for recent influenza-like illness in 41 patients (11%). The prevalence of influenza and influenza-like-illness in our ACS population was approximately 23%, which is much higher than the 0.01% prevalence reported by the Ministry of Public Health for the general Thai population (Ministry of Health, 2007). This may be explained by under diagnosis on national surveillance and/or the benign and self-limited nature of influenza in the general population. The increase in frequency of occurrence of influenza in cardiac patients in winter time was similar to other published reports (Glezen *et al,* 1982; Sheth *et al,* 1999) The results of this study are consistent with others that influenza can trigger ACS (Madjid *et al,* 2007a,b), and suggest that the prevalence of influenza infection in patients in Thailand presenting with ACS is sufficient to warrant vaccination as a prevention measure.

Influenza has never been proven as a definite cause of ACS. Only one study has established a possible connection between acute systemic infection and increasing inflammatory cells in human atherosclerotic arteries (Madjid *et al,* 2007a). However, there is indirect evidence from clinical studies suggesting a protective role of influenza vaccination against the development of coronary artery disease (Madjid *et al,* 2007b) and the risk of hospitalization from cardiac disease (Nichol *et al,* 2003).

The use of influenza vaccine in Thailand is limited. There is no recommendation for influenza vaccination in the elderly or in patients with cardiovascular disease. This could reflect the perception of the Ministry of Public Health that influenza and its complications are relatively rare and thus vaccination is not cost-effective. The prevalence of influenza in the ACS population in our study was nearly 25%, and if an etiologic relation to ACS among these patients can be shown, then influenza vaccination could be very protective in these high risk patients, with only a small number of patients needing to be vaccinated in order to prevent one ACS.

Our study was limited by the absence of a control population. The prevalence of influenza and influenza-like illness in those without ACS during the same time period is assumed, given available surveillance data, but not measured. Our data does indicate a sufficiently high prevalence of influenza in this specific group of patients, higher than expected, and does support the hypothesis that influenza may be associated with acute coronary syndrome.

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