Original Article

Serologic Prevalence of Syphilis in Acute Ischemic Stroke

Lanamtieng T, MD[1,2], Kasemsap N, MD[1,2], Meesing A, MD[1,3]

[1] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] North-eastern Stroke Research Group, Khon Kaen University, Khon Kaen, Thailand
[3] Sleep Apnea Research Group, Research Center in Back and Other Joint Pain and Human Performance, Research and Training Center for Enhancing Quality of Life of Working Age People, and Research and Diagnosis Center of Emerging Infectious Diseases (RCEID), Khon Kaen University, Khon Kaen, Thailand

Background: Syphilis is a sexual-transmitted infectious disease that can cause stoke in elderly, called neurosyphilis.

Objective: The authors determined the serologic prevalence of syphilis and associated factors in acute ischemic stroke (AIS) patients.

Materials and Methods: A prospective cross-sectional study was performed during 1 September 2015 to 31 January 2017. A total 466 patients who admitted in stroke unit of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, were included. Syphilis serologic test (VDRL and TPHA) were tested. Data regarding, age, gender, severity (NIHS score), stroke classification (TOAST) were collected to assess factors influencing seropositive patients. Seropositive patients were defined as the patients who had positive test for VDRL and/or TPHA.

Results: Of 466 AIS patients tested. The serologic prevalence of syphilis in AIS patients was 12.6%. Median age was 75.2 years (IQR 70.3 to 84.2) in seropositive patients, compare to seronegative patients which had 63.7 years (IQR: 54.9 to 74.0, $p<0.01$]. Other associated factors, such as gender, severity (NIHS score), and TOAST could not show statistically significant.

Conclusion: Syphilis in AIS patients in Khon Kean was modest, therefore, clinician should perform syphilis serologic test in elderly AIS patients.

Keywords: Syphilis, Neurosyphilis, Ischemic stroke, Cerebrovascular accident

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Atherosclerosis is the most common cause of ischemic strokes in high risks patient. It is often associated with patients who are at risk for vascular diseases, such as elderly patients or those with metabolic conditions. Syphilis is a sexually transmitted disease or vertical transmission during pregnancy caused by *Treponema pallidum* subspecies *pallidum* (*T. pallidum*). *T. pallidum* infection causes local inflammation due to immune response against spirochetes replication resulting in mimicking other diseases. After primary infection, *T. pallidum* has long latent period without any symptoms[1-3]. Neurosyphilis is an infection that causes neurological symptoms including amnesia, abnormal movements, and stroke. Symptoms can manifest shortly after the infection or many years afterwards[1]. Currently, syphilis is less common since the advent of effective antibiotic treatment. The syphilitic patients, who are being found presently, are most likely elderly. Moreover, they would have most likely forgotten having been infected in the past when there was a higher prevalence of the disease[1, 4-7].

Diagnosis of neurosyphilis remains a challenge due to the frequent atypical presentations that are often indistinguishable from other diseases. The prognosis can be very good, with almost complete recovery if the appropriate therapy is started early. Typically, neurosyphilis is described as a late manifestation, but neuroinvasion and neurological disease occur in both early and late syphilis[4,6].

A diagnosis of neurosyphilis is based on the presence of symptoms associated with the detection of syphilis in the cerebrospinal fluid. Because the treatment focuses more on the atherosclerosis, the detection other causes of acute ischemic stroke, such as neurosyphilis are often neglected. The treatment has benefit to prevent further complication of neurosyphilis. The authors determined the serologic prevalence of syphilis in stroke patient and associated factors in acute ischemic stroke (AIS) patients.

Materials and Methods

A prospective cross-sectional study was performed during 1 September 2015 to 31 January 2017. Patients 18 years of age and over, who had experienced an acute ischemic stroke and who admitted to the stroke unit of

Correspondence to:
Meesing A.
Department of Medicine, Faculty of Medicine, Khon Kaen University, 123 Mitraparp Highway, Khon Kaen 40002, Thailand.
Phone: +66-43-363664, **Fax:** +66-43-348399
E-mail: atibordee@kku.ac.th

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tertiary hospital, Khon Kaen University, were included. All AIS patients were tested for syphilis serologic. Patients who had serum positive for Venereal Disease Research Laboratory (VDRL) or Treponema Pallidum Hemagglutination Assay (TPHA) were considered as syphilis-infected patients. The cerebrospinal fluid (CSF) is examined in patients who had reactive serum VDRL or TPHA. Patients with abnormal CSF cell count and/or protein, including reactive CSF-VDRL, were diagnosed as neurosyphilis.

Furthermore, other data were collected to examine factors which are related to the disease including the following: age, sex, classification of acute ischemic stroke (TOAST classification)[8], and the severity of ischemic stroke (National Institutes of Health Stroke Score, NIHS score)[9].

Statistical analysis

The sample size of 466 participants was based on an 8% anticipated prevalence that has been reported previously[10] with one sided alpha level of 0.05 and 80% power. Descriptive statistics were calculated to present the data. Categorical data were reported as percentages; continuous data were reported as means $\pm$ standard deviations, if normally distributed, and as medians with ranges, if not normally distributed. Missing data for the variables of interest were negligible. The Chi-square test or Fisher's exact test were used to compare categorical variables. Bivariate correlation analyses were performed using Pearson or Spearman tests for nonparametric variables. The 2-tailed statistical significance level was $p<0.05$. Associations were expressed as hazard risk (HR) or odd ratio (OR) and 95% confidence interval (95% CI). Univariate survival curves were calculated using the Kaplan-Meier method, and differences in survival rates between groups were analyzed by the log-rank test. All analyses were performed with SPSS version 19.

Results

Baseline characteristic of patients

During the study period, a total of 466 patients with AIS patients were investigated. Of these, 58.7% were males. The median age of the patient cohort was 65.1 years (IQR 55.9 to 79.4). The most cause of stroke by TOAST classification were small vessel occlusion (57.8%), large artery atherosclerosis (12.5%), and cardioembolism (11.4%). Thrombolytic treatment with r-TPA was observed in 45 patients (11.9%). The seropositive of syphilis in AIS patients was observed in 58 patients (12.6%). Lumbar puncture was performed in only 3 patients. Of these, 1 patient had neurosyphilis revealed by abnormal protein in CSF, but negative result from VDRL. The baseline characteristics are listed in Table 1.

Factors associated with seropositivity

The seropositive patients have statistically significant higher of median age compared to seronegative patients (74.0 years [IQR 54.9 to 74.0] vs. 63.7 years [IQR 54.9 to 74.0], OR 1.08 [95% CI 1.05 to 1.11], $p<0.01$). The

Table 1. Demographic of patient with acute ischemic stroke

Baseline characteristics	n
Male (%)	270 (58.7)
Median age (years), (IQR)	65.1 (55.9 to 79.4)
Patients receiving r-TPA (%)	45 (11.9)
Median NIHS score (IQR)	6.5 (1 to 8)
Median HDL (mg/dL), (IQR)	46.5 (36 to 56)
Median LDL (mg/dL), (IQR)	124.7 (92 to 156)
Median WBC (cell/ mm^3), (IQR)	8,250 (6,300 to 9,500)
TOAST classification, (%)	
Small vessel occlusion	266 (57.8)
Large artery atherosclerosis	58 (12.5)
Cardioembolism	53 (11.4)
Stroke of undetermined etiology	6 (1.3)
Stroke of other determined etiology	3 (0.6)

r-TPA = Recombinant tissue plasminogen activator; NIHS = National Institutes of Health Stroke; HDL = High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol; WBC = White blood cell count; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Table 2. Univariate analysis of factors associated with seropositive in patients with acute ischemic stroke

Factors	Seropositive (n = 58)	Seronegative (n = 402)	Odds ratio	*p*-value
Age median (IQR)	75.2 (70.3 to 84.2)	63.7 (54.9 to 74.0)	1.08 (1.05 to 1.11)	<0.01
Male (%)	36 (62.1)	234 (58.2)	1.17 (0.67 to 2.1)	0.58
Median NIHS score (IQR)	4.75 (1 to 4)	6.74 (1 to 9)	0.97 (0.91 to 1.03)	0.29
TOAST classification (%)				
Cardioembolism	9 (15.5)	44 (10.9)		
Small vessel occlusion	37 (63.8)	229 (57.0)	0.79 (0.36 to 1.75)	0.56
Large artery atherosclerosis	6 (10.3)	58 (14.4)	0.56 (0.38 to 1.71)	0.31
Stroke of undetermined etiology	0	6 (1.5)	-	-
Stroke of other determined etiology	1 (1.7)	2 (0.5)	2.44 (0.20 to 1.71)	0.48

NIHS = National Institutes of Health Stroke Score; TOAST = Trial of Org 10172 in Acute Stroke Treatment

NIHs score of seropositive patients trend to lower compared to seronegative patients (4.75 [IQR 1 to 4] vs. 6.74 [IQR 1 to 9], OR 0.97 [95% CI 0.91 to 1.03], $p = 0.29$). Patients with seropositive tend to have higher chance of stroke by other determined etiology and TOAST classification (OR 2.44, [95% CI 0.20 to 1.71], $p = 0.48$).

Discussion

Regarding the present study, it was revealed that the prevalence of THPA positive in the serum was 8.34% in previous study by Dharmasaroja et al in Thailand[10]. However, when compared to a study conducted overseas in Australia by Cordato et al[5], the prevalence in Thailand was found to be higher. This is due to the fact that there used to be a syphilis epidemic in Thailand. In addition, due to the insufficient quality of public healthcare systems, the disease has been found to be more common in developing countries than in developed countries[11-13].

Regarding the factors related to detecting syphilis in the blood of patients having had acute ischemic strokes, the seropositive patients showed a significantly higher median age than the group without syphilis. This can be explained by the fact that in the past, syphilis was more prevalent than in the present and that when people became infected in the past the disease would remain with them throughout their lives. Therefore, for people, who lived during the time of the epidemic, syphilis was only detected through a VDRL or a TPHA.

Even if the VDRL and TPHA tests do not indicate the severity of the infection and cannot determine whether neurological symptoms are caused by syphilis, they are considered as a preliminary examination. This is a guideline for evaluating whether additional tests are needed to confirm a diagnosis in a more detailed way.

The drawback of the present study is the lack of information regarding the history of treatment or previous infections of the patients. The information is difficult to record because the patients had contracted syphilis when they were young, but only when the patients had reached middle-age or had become elderly had the disease manifested itself in an acute ischemic stroke.

In addition, the present study was unable to indicate whether or not the acute ischemic stroke in the seropositive patients had been the result of neurosyphilis or late latent syphilis because of lack of CSF examination data since it has contraindication to perform lumbar puncture. Dharmasaroja et al[10] found that patients with ischemic stroke having syphilis had received CSF examination and that 29 percent of them had proven to have neurosyphilis. The study indicated that in such patients, it is important to examine by CSF.

The advantages of the present study are its distinctive methodology in finding the serologic prevalence and the fact that it is also a prospective study. Although previous studies have somewhat reported on the prevalence of syphilis in patients with ischemic stroke, none of them has calculated the sample size based on statistics. In order to raise awareness of other causes of ischemic stroke, the present study has highlighted the problem so that patients, especially those with syphilis can be correctly diagnosed and properly treated.

Additional studies should be preformed, more attention should be paid to finding the relationship between syphilis in the blood and neurosyphilis in patients with acute ischemic stroke.

Conclusion

Once, Thailand was one of the epidemic areas for syphilis. As a result, the findings of this study revealed a serologic prevalence of syphilis was 12.6% among patients with acute ischemic stroke. This raises awareness in regard to finding other causes of acute ischemic stroke especially in elderly patients whose symptoms are often ignored, which can lead them to be misdiagnosed with other illnesses.

What is already known on this topic?

The prevalence of positive serum TPHA was 8.34% in Thai acute ischemic stroke patients.

What this study adds?

Syphilis should be considered as one contributing factor in Thai acute ischemic stroke patients particularly the elderly.

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Potential conflicts of interest

The authors declare no conflict of interest.

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